Synthesis of Optically Active Fjord-Region 11,12-Diol 13,14-Epoxides and the K-Region 9,10-Oxide of the Carcinogen Benzo[g]chrysene

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Received November 18, 1988

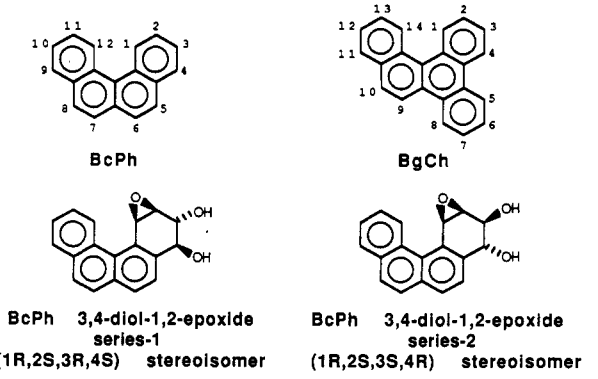
Optically pure enantiomers of the diastereomeric pair of benzo[g]chrysene-11,12-diol 13,14-epoxides (Scheme VI) were synthesized from (11*R*,12*R*)- and (11*S*,12*S*)-dihydroxy-11,12-dihydrobenzo[g]chrysenes (**16(R,R)** and **16(S,S)**). Two routes were employed to synthesize the racemic dihydrodiol **16**. Although the Prevost method for introduction of the trans-vicinal oxygen atoms at C_{11} and C_{12} of 13,14-dihydrobenzo[g]chrysene (**7**) proceeded poorly, introduction of the trans-vicinal oxygen atoms was readily achieved by hydration of the tetrahydro 11,12-epoxide (**9**, Scheme II) or by $NaBH_4$ reduction of benzo[g]chrysene-11,12-dione (**17**, Scheme IV). The latter method is the most effective for the synthesis of the racemic dihydrodiol **16**, whereas the former method is preferred for the preparation of substantial amounts of the enantiomers of **16** since the diastereomeric bis-(−)-menthyloxy esters of the tetrahydrodiol **11** (Scheme V) are much more effectively separated by HPLC than are the corresponding derivatives of the dihydrodiol **16**. The conformational preference of the hydroxyl groups in the series-1 diol epoxide in which the benzylic 11-hydroxyl group and the epoxide oxygen are cis (**19**, Figure 2) was found to be dependent upon solvent, with a quasidiequatorial conformation being preferred in DMSO-d_6 and a quasidiaxial conformation being preferred in $CDCl_3$. As anticipated from prior studies of the rates of hydrolysis of the 3,4-diol 1,2-epoxides of benzo[c]phenanthrene, the present 11,12-diol 13,14-epoxides are relatively stable in neutral, aqueous media. Enantiomers of the K-region 9,10-oxide **24** were prepared from benzo[g]chrysene (Scheme IX). The K-region bromohydrin, obtained by reduction of the K-region bromo acetate with DIBAL-H, was converted to a pair of diastereomeric esters with (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. After separation by HPLC, the MTPA bromo esters were treated with NaOMe to provide the enantiomers of **24**. NaOMe was found to open **24** by preferential attack at C_{10}, although C_9 is calculated to be the more reactive position.

For more than 50 years, scientists have been attempting to elucidate the structural factors involved in polycyclic aromatic hydrocarbon (PAH) carcinogenesis.[1] In the 1970s, it was discovered that metabolism to bay-region diol epoxides was associated with high mutagenicity and carcinogenicity for carcinogenic PAHs.[2] Since then, a large number of diol epoxides have been studied, and a number of factors have been found to contribute to their mutagenicity and carcinogenicity. The presence of the epoxide moiety in a bay region has been found to be a requirement for high activity of diol epoxides derived from alternant PAHs. Among the bay-region diol epoxides, reactivity, conformation, and absolute configuration have been shown to contribute to mutagenicity and carcinogenicity.[3,4]

Of the diol epoxides studied in recent years, the "fjord-region" diol epoxides of benzo[c]phenanthrene (BcPh, Chart I) are among the most interesting. They exhibit conformational characteristics different from the bay-region diol epoxides of other alternant PAHs, in that both the series-1 (benzylic OH and oxirane oxygen atom cis) and series-2 (benzylic OH and oxirane oxygen atom trans) diol epoxides have conformations in which the hydroxyl groups strongly prefer the quasidiequatorial conformation.[5] Series-1 bay-region diol epoxides from other alternant PAHs prefer (moderately or strongly) a conformation with quasidiaxial hydroxyl groups. Interestingly, the 1*R*,2*S*,3*R*,4*S* series-1 fjord-region diol epoxide of BcPh is unique among series-1 diol epoxides in that it has high tumorigenicity in mouse skin which is comparable to that of the series-2 isomer.[6a] For other carcinogenic alternant PAHs, only the series-2 stereoisomer of *R*,*S*,*S*,*R* absolute configuration has shown high tumorigenicity.[4]

In order to better understand the structural factors affecting fjord-region diol epoxide mutagenicity and tumorigenicity, we have synthesized the enantiomers of the series-1 and series-2 benzo[g]chrysene-11,12-diol 13,14-epoxides (cf. Scheme VI). Benzo[g]chrysene (BgCh, Chart I) is a potent carcinogen and, unlike BcPh, possesses two distinguishable fjord regions due to its lack of symmetry. In previous work, we reported the synthesis of the BgCh

Chart I. Structural Formulas for BcPh and BgCh and Series-1 and Series-2 BcPh Fjord-Region Diol Epoxides



† University of Oklahoma.
‡ The National Institutes of Health.

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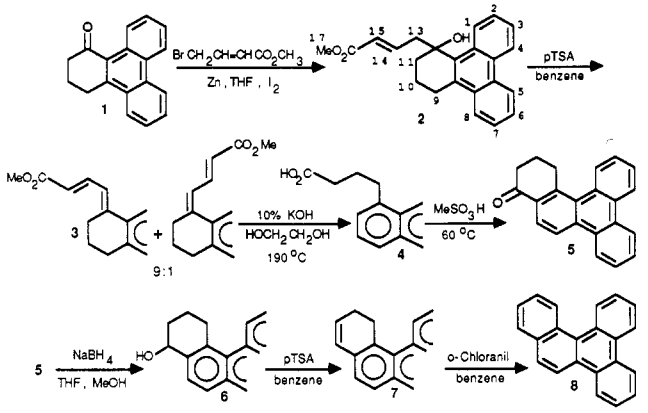
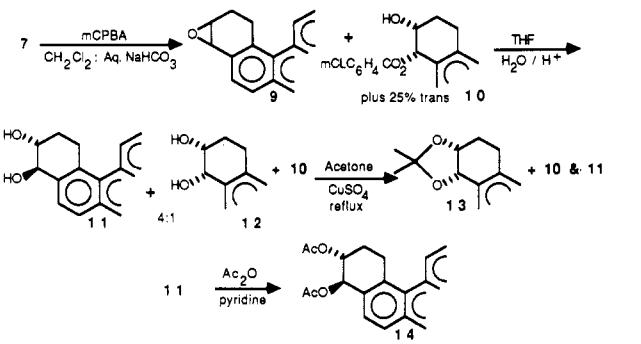
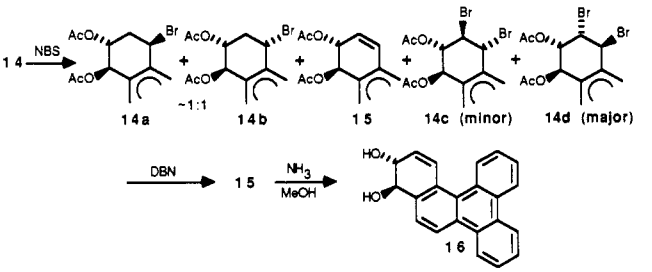
Scheme I



Scheme II



Scheme III



3,4-diol 1,2-epoxides, which were expected and found to prefer conformations with quasidiaxial hydroxyl groups, due to the steric interaction with the 5,6,7,8-benzo ring.[7] The BgCh 11,12-diol 13,14-epoxides, on the other hand, are structurally more analogous to the carcinogenic BcPh 3,4-diol 1,2-epoxides, in that the steric interaction between the benzylic hydroxyl groups and an adjacent angular benzo ring is absent. The BgCh 11,12-diol 13,14-epoxides are predicted to be ultimate carcinogens and are expected to be formed metabolically, since their immediate metabolic precursor, BgCh 11,12-dihydrodiol (**16**, Scheme III), has been shown to be the major dihydrodiol metabolite of BgCh.[8] Tumor studies of the BgCh diol epoxide enantiomers will provide insight into whether the stereochemical relationships with tumorigenicity observed for the BcPh diol epoxides extend to other fjord-region diol epoxides.

Results and Discussion

Fjord-Region Diol Epoxides. Synthesis of the diol epoxides began with the preparation of the 11-keto derivative of BgCh **5** and its conversion to the 13,14-dihydro derivative (**7**, Scheme I). The first step involved a vinylogous Reformatsky reaction which produced alcohol **2** from the reaction of triphenylene ketone **1** with the zinc enolate of methyl 4-bromocrotonate. Optimal results were obtained in THF as solvent with a large excess of Zn and, most importantly, the dropwise addition of 2 equiv of bromocrotonate over 2 h, followed by immediate quenching of the reaction. The initial adduct is formed reversibly, and longer reaction times result in reversion to **1** and side products from reaction with the bromocrotonate. These results are consistent with recent studies of the vinylogous Reformatsky reaction.[9,10] The product of this reaction was not normally purified due to decomposition, but instead the crude alcohol **2** was dehydrated by stirring at room temperature with *p*-toluenesulfonic acid (*p*-TsOH) in benzene. This resulted in complete conversion of **2** to the diene esters **3**, which were used without purification. The diene esters were hydrolyzed and isomerized by heating to 180–190 °C in 10% KOH in ethylene glycol for 12 h. The resulting 1-triphenylenebutyric acid **4** was cyclized to the 11-keto derivative **5** by stirring in $MeSO_3H$[11] at 55–60 °C for 4 h. The ketone was then purified by chromatography on silica gel and isolated in 55–60% overall yield from triphenylene ketone **1**. Conversion of ketone **5** to the alkene **7** was achieved by sodium borohydride reduction of the ketone to alcohol **6** followed by dehydration (*p*-TsOH). The alkene was purified by chromatography on silica gel and isolated in 85% yield from the ketone. In order to confirm the ring structure and to supply material for biological testing, some of the alkene was converted to the parent hydrocarbon **8** by reaction with *o*-chloranil. The product obtained was identical with that previously described.[12]

Two methods were developed for conversion of alkene **7** to dihydrodiol **16** (Scheme III), the first involving conversion of the alkene to the *trans*-diacetate (**14**, Scheme II). Attempts to use the Prevost reaction (AgOAc and I_2) to directly convert the alkene to the diacetate were not successful, producing several side products and isolated yields of less than 20%. The method that was used to make the diacetate (Scheme II) involved synthesizing the tetrahydro epoxide **9** by reaction of the alkene with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by opening of the epoxide to the tetrahydrodiol **11**. Since epoxidation in CH_2Cl_2 resulted in extensive formation of adduct **10** with *m*-chlorobenzoic acid, the reaction was run in a vigorously stirred two-phase mixture of CH_2Cl_2 and aqueous $NaHCO_3$.[13] This produced complete conversion to the epoxide with only 5–10% of **10** being formed. When the crude epoxide was opened to the tetrahydrodiol, the ratio of

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Table I. Partial ^1H NMR Spectral Data for the Products of the NBS Reaction[a]

	H_{11}	H_{12}	H_{13}	H_{14}
14a	d, 7.10	m, 5.12–5.17	–	t, 6.10
		($J_{11,12}$ = 8.0, H_{14} J_{app} = 3.7)		
14b	d, 6.37	p, 5.99	–	t, 6.26
		($J_{11,12}$ = 4.3, H_{12} J_{app} = 5.2, H_{14} J_{app} = 3.8)		
14c	d, 7.01	d, 5.45	d, 4.69	d, 6.21
		($J_{11,12}$ = 7.9, $J_{13,14}$ = 2.0, $J_{12,13}$ ~ 0)		
14d	d, 6.65	dd, 6.10	t, 5.12	d, 7.04
		($J_{11,12}$ = 7.6, $J_{12,13}$ = 3.2, $J_{13,14}$ = 3.8)		
15	d, 6.34	m, 5.70–5.76	dd, 6.21	d, 7.41
		($J_{11,12}$ = 6.7, $J_{12,13}$ = 4.0, $J_{13,14}$ = 10.2)		

[a] Spectra were measured in $CDCl_3$–CCl_4 at 300 MHz, chemical shifts in parts per million and coupling constants (J) in hertz.

trans- to *cis*-diol was 4:1. The *cis*-diol **12** was converted to the acetonide **13** by reaction with copper sulfate in acetone, and the mixture of **10**, **11**, and **13** was then separated by chromatography on silica gel. The tetrahydrodiol **11**, isolated in 60–70% yield, was cleanly converted to the diacetate **14** in 95% yield with Ac_2O in pyridine.

Attempts to introduce the double bond between C_{13} and C_{14} by reacting the diacetate with DDQ were of little success, with much aromatized material being formed. Benzylic bromination of the diacetate at C_{14} with NBS followed by dehydrobromination with DBN was found to be a convenient way to introduce the double bond. The NBS reaction produced a mixture of mono- and dibrominated products (Scheme III), all of which were converted to the dihydrodiol diacetate **15** upon reaction with DBN. Partial NMR data for these brominated products are given in Table I. Several observations were made concerning the bromination reaction: (1) excess NBS is required for complete reaction; (2) the monobrominated products are only observed in NMR spectra of samples taken directly from the reaction flask; (3) if the reaction is allowed to run for 24 h, only the dibrominated products are present; (4) attempts to isolate the bromination products produced inconsistent results; and (5) consistent results were obtained only when the bromination reaction mixture was not worked up but rather reacted directly with DBN. These results are consistent with dehydrobromination of the initial monobromo products during reaction and workup, with the HBr generated during workup leading to various degrees of decomposition and therefore variable yield. The alkene **15** generated by dehydrobromination during reaction is brominated to form the dibromo derivatives. Treatment of the crude bromination products directly with DBN dehydrobrominates the monobrominated compounds and debrominates the dibrominated compounds, thus avoiding any decomposition during workup. Dehalogenation by DBN is not surprising as other amines have also been used for this purpose.[14]

The crude dihydrodiol diacetate **15** was unstable to chromatography, so it was hydrolyzed (NH_3-saturated MeOH) to the dihydrodiol **16**, which was then purified by chromatography on silica gel. The isolated yields of the pure dihydrodiol from **14** were consistently between 46 and 50%. NMR analysis (C_6D_6) of the dihydrodiol revealed an 11.6-Hz coupling constant between H_{11} and H_{12}, which indicates that the hydroxyl groups prefer a pseudodiequatorial conformation. This dihydrodiol was also found to be identical with the major dihydrodiol formed upon metabolism of the parent hydrocarbon.[8]

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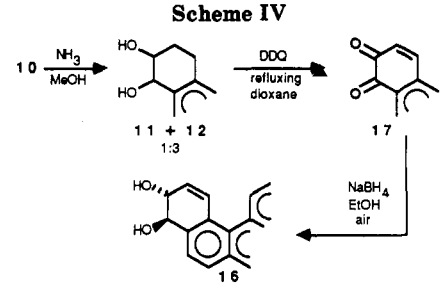
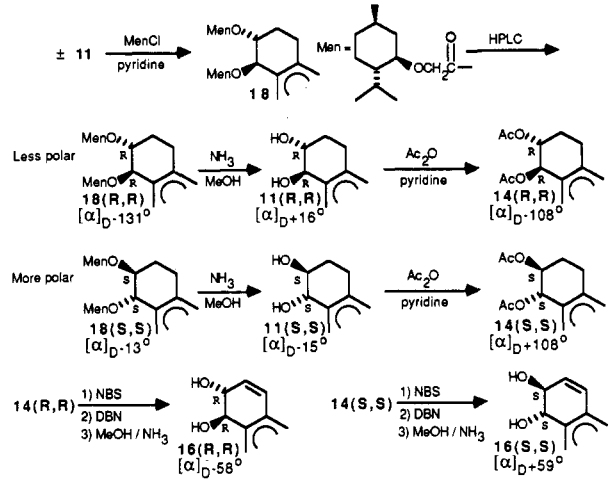
Scheme IV



Scheme V



The second method for preparation of the dihydrodiol utilized adduct **10**. Hydrolysis of **10** provided a mixture of the tetrahydrodiols **11** and **12**, which (Scheme IV) were oxidized to BgCh 11,12-dione **17** in 75% yield by reaction with DDQ in refluxing *p*-dioxane. The quinone was converted to the *trans*-dihydrodiol **16** by sodium borohydride reduction[15–17] (70% yield). Reduction of the quinone proved to be the most convenient way to prepare racemic dihydrodiol.

Enantiomerically pure dihydrodiols were made via the bromination pathway after HPLC separation of the diastereomeric bis-(−)-menthyloxy esters of the *trans*-tetrahydrodiol **11** (Scheme V). The separation of the tetrahydrodiol diesters was much better than that of the dihydrodiol diesters (α = 1.45 vs 1.28; 0.45 × 25 cm silica gel, 4.5% Et_2O–hexane, 6.0 mL/min). Preparative HPLC (α = 1.36) provided the less polar diastereomer **18(R,R)**, $[\alpha]^{18}_D$ −131°, in 81% yield from the tetrahydrodiol and the more polar diastereomer **18(S,S)**, $[\alpha]^{18}_D$ −13°, in 85% yield. The *R,R* and *S,S* assignments were initially made on the basis of the NMR spectra of the diastereomers, which gave a set of singlets for the ester methylene groups (OCOCH_2O) of the less polar diastereomer **18(R,R)** and a set of AB quartets for the more polar diastereomer **18(S,S)**. The NMR results, sign and magnitude of rotation, and order of elution parallel those observed for other bis-(−)-menthyloxy esters of dihydro- and tetrahydrodiols of the PAH.[18,19] The *R,R* isomer for these derivatives has always been the less polar diastereomer having the more negative value of $[\alpha]_D$. Unambiguous assignment of configuration was made by using the exciton chirality method.[20] The

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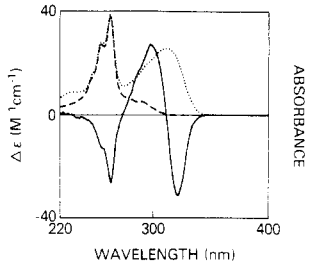
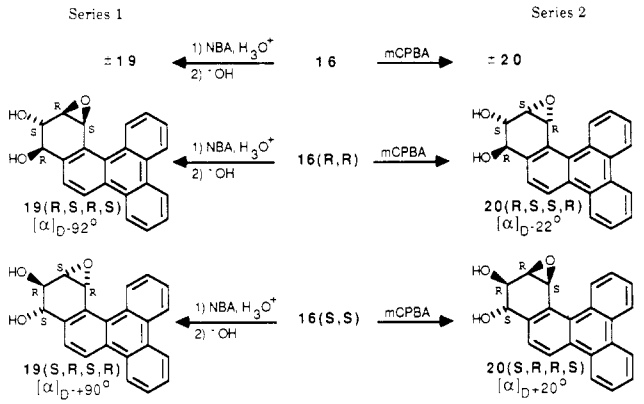
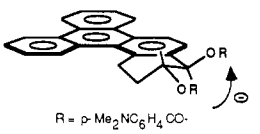


Figure 1. CD spectrum of the 11,12-bis(4-(dimethylamino)-benzoate) from the tetrahydrodiol of the less polar bismenthyloxy ester (solid) along with its UV spectrum (dotted) and the UV spectrum of the tetrahydrodiol (dashed, ϵ_{264nm} = 90 000) all determined in acetonitrile.

Scheme VI



less polar diastereomer was hydrolyzed (NaOMe in THF–MeOH (1:1)) to the tetrahydrodiol, which was then reacted with 4-(dimethylamino)benzoyl chloride, producing the 11,12-bis(4-(dimethylamino)benzoate) **21**. The circular dichroism spectrum of this compound exhibited a pair of strong, fairly symmetric Cotton effects with a negative band at 322 nm, a zero at 312 nm, and a positive band at 299 nm (Figure 1). The negative value of $\Delta\epsilon_{322nm}$ = −31.4 M^{-1} cm^{-1} obtained at the longer wavelength indicates that a left-handed helicity exists between the two electric dipole moments and requires an 11*R*,12*R* absolute configuration



of the dibenzoate esters. Therefore, the less polar menthyloxy ester diastereomer has 11*R*,12*R* absolute configuration. The menthyloxy diastereomers (Scheme V) were then hydrolyzed (NH_3 in MeOH), producing the enantiomerically pure tetrahydrodiols **11(R,R)** and **11(S,S)**, which were acetylated to give the enantiomerically pure diacetates **14(R,R)** and **14(S,S)**. The diacetates were then converted to the dihydrodiols **16(R,R)** and **16(S,S)** by the bromination method.

Synthesis of the racemic and enantiomerically pure diol epoxides was achieved by conventional methods[21] (Scheme VI). The series-1 diol epoxides **19** were prepared, via their bromo triols, in 80–90% yields while the series-2 diol epoxides **20** were prepared directly from their dihydrodiols with *m*-CPBA in 70–95% yields. NMR analysis revealed that both the series-1 and series-2 diol epoxides preferred a pseudodiequatorial conformation for their hydroxyl

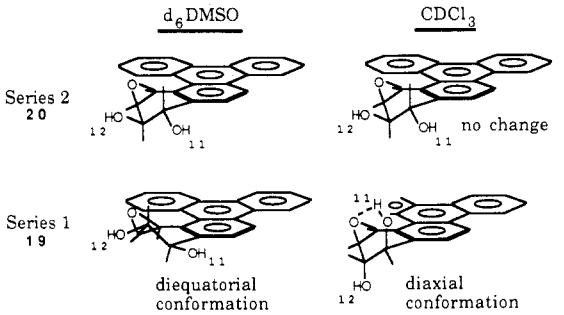


Figure 2. Conformations of the series-1 and series-2 diol epoxides of BgCh in DMSO-d_6 and $CDCl_3$.

Table II. Hydroxyl ^{1}H NMR Spectral Data for the Series-1 and Series-2 Diol Epoxides in DMSO-d_6 and $CDCl_3$

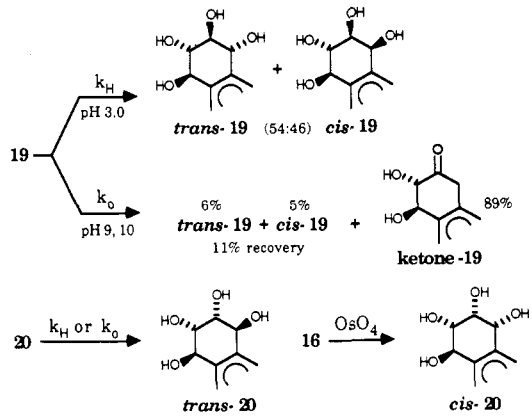
	DMSO-d_6		$CDCl_3$	
	δ, ppm (*J*, Hz)	$\Delta\delta$	δ, ppm (*J*, Hz)	$\Delta\delta$
	Series 1			
OH_{11}	5.75 (6.2)	0.09	2.89 (10.6)	1.18
OH_{12}	5.84 (4.8)		1.71 (7.4)	
	Series 2			
OH_{11}	5.83 (6.2)	0.16	2.69 (4.7)	0.10
OH_{12}	5.67 (4.9)		2.59 (6.2)	

groups ($J_{11,12}$ = 8.7 Hz for series 1, $J_{11,12}$ = 8.8 Hz for series 2; DMSO-d_6). This is the second example of a series-1 diol epoxide that prefers this conformation, the other being the diol epoxide of BcPh.[5] Optical rotations for members of the enantiomeric pairs were equal but of opposite rotation (schemes and Experimental Section). Interestingly, the series-2 *R,S,S,R* enantiomers from both BcPh and BgCh (fjord-region diol epoxides) have negative values of $[\alpha]_D$ unlike their bay-region analogues from several other hydrocarbons.[22]

When the NMR spectra of the diol epoxides were taken in $CDCl_3$ instead of DMSO-d_6, the coupling constant between H_{11} and H_{12} showed little change for the series-2 diol epoxide, but dropped to 3.3 Hz for the series-1 diol epoxide. This indicates a major change in conformation for the series-1 diol epoxide in this solvent. This change was highly solvent sensitive in that only 2–3 drops of MeOH-d_4 in 0.5 mL of $CDCl_3$ raised the coupling constant from 3.3 to 5.6 Hz. The hydroxyl protons (OH_{11} and OH_{12}) also showed changes when the NMR spectrum of the series-1 diol epoxide was taken in $CDCl_3$ (Table II). The larger coupling constant for OH_{11} indicates a substantial change in the dihedral angle between OH_{11} and H_{11}. There is also a much larger difference in the chemical shifts of OH_{11} and OH_{12} than that observed in DMSO-d_6 or for the hydroxyl groups of the series-2 diol epoxide in either solvent. One explanation for the change in conformation may be that when there is no solvent to which the hydroxyl groups can hydrogen bond, the series-1 diol epoxide hydrogen bonds internally. The conformations shown in Figure 2 indicate how the series-1 diol epoxide might change its conformation by forming a hydrogen bond between OH_{11} and the oxygen of the epoxide. Since this interaction is not possible in the series-2 diol epoxide, no change in conformation would be expected. This interaction can also explain the larger coupling constant between OH_{11} and H_{11} because of the large dihedral angle that would exist between them in this conformation. Internal hydrogen bonding between OH_{11} and the epoxide oxygen atom can also explain the larger difference in the chemical shifts of OH_{11} and OH_{12}.

(20) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257–263.
(21) Yagi, H.; Hernandez, O.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 6881–6883.
(22) Yagi, H.; Thakker, D. R.; Ittah, Y.; Croisy-Delcey, M.; Jerina, D. M. *Tetrahedron Lett.* **1983**, *24*, 1349–1352.

Scheme VII



The decrease in internal hydrogen bonding of OH_{12} to OH_{11} would cause the observed upfield shift of OH_{12}. Because of the relationship between conformation of diol epoxides and their carcinogenicity,[6] it is important to note that this series-1 diol epoxide changes conformation depending upon its environment.

Kinetics and Products of Diol Epoxide Hydrolysis. Diol epoxides studied to date have been observed to undergo hydrolysis in aqueous solution following the rate law

$$k_{obsd} = k_H a_{H^+} + k_0$$

Thus, plots of log k_{obsd} vs pH are biphasic and exhibit a first-order dependence on hydronium ion (k_H) at low pH values and a pH-independent process (k_0) that becomes dominant at pH values near or slightly above neutrality. As expected, the diol epoxides of BgCh also undergo hydronium ion catalyzed (k_H, measured at pH 3.6–5.3) and pH-independent solvolysis (k_0, pH 9–10) in 1:9 dioxane–water, ionic strength of 0.1 M ($NaClO_4$), at 25 °C. The values of k_H for **19** and **20** were 72 and 169 M^{-1} s^{-1}, respectively, and the values for the spontaneous hydrolysis (k_0) were 7.9 ± 0.2 × 10^{-6} s^{-1} ($t_{1/2}$ ~ 24 h) and 6.7 ± 0.7 × 10^{-7} s^{-1} ($t_{1/2}$ ~ 287 h). The break points in the biphasic pH–rate profiles for these diol epoxides based on the above equation occur at pH 8.0 and 8.4, respectively. As in the cases of BcPh and a number of other diol epoxides, k_H is larger for diol epoxide-2 isomers than for diol epoxide-1, whereas k_0 is larger for diol epoxide-1 than for diol epoxide-2. Thus, the plots of log k_{obsd} vs pH cross. The magnitudes of the rates are consistent with estimates ($\Delta E_{deloc}/\beta$)[23] of the ease of formation of a carbonium ion at C_{14} ($\Delta E_{deloc}/\beta$ = 0.586) and are very similar to those of the fjord-region diol epoxides of BcPh[5] which are closely related in structure and calculated reactivity.

Products from acidic hydrolysis (pH 3.0) of **19** were the *trans*-**19** and *cis*-**19** tetrols in nearly equal amounts, while **20** produced only the *trans*-**20** tetrol (Scheme VII). Spontaneous hydrolysis (pH 9 and 10) of **19** also gave *trans*-**19** and *cis*-**19** in similar amounts, but only 11% of the diol epoxide was recovered as tetrol. The majority of **19** was presumably converted to ketone-**19** as was the case for the series-1 diol epoxide of BcPh.[5] Spontaneous hydrolysis of diol epoxide **20** quantitatively produced *trans*-**20** tetrol. Since no *cis*-tetrol was detected in the hydrolysis of **20**, authentic *cis*-**20** was synthesized from dihydrodiol **16** by treatment with OsO_4. Assignment of structure of the *cis*- and *trans*-tetrol isomers was achieved by NMR analysis of the methine protons of the corresponding tetrol tetraacetates (Table III) whose spectra are similar to those from BcPh.[5]

Table III. Partial ^{1}H NMR Spectral Data of the Tetrol Tetraacetates from Diol Epoxides 19 and 20[a]

compound	methine protons			
	H_{11}	H_{12}	H_{13}	H_{14}
trans-**19** tetraacetate	6.69 ($J_{11,12}$ = 8.3,	5.20 $J_{12,13}$ = 2.7,	5.41 $J_{13,14}$ = 3.7)	6.78
cis-**19** tetrol tetraacetate	6.38 ($J_{11,12}$ = 3.6,	5.85 $J_{12,13}$ = 9.7,	5.06 $J_{13,14}$ = 2.2)	7.19
trans-**20** tetrol tetraacetate	6.45 ($J_{11,12}$ = 6.1,	5.71 $J_{12,13}$ = 2.5,	5.74 $J_{13,14}$ = 5.6)	6.91
cis-**20** tetrol tetraacetate[b]	6.67 ($J_{11,12}$ = 8.4,	5.71 $J_{12,13}$ = 2.3,	5.84 $J_{13,14}$ = 3.5)	*c*

[a] Spectra were measured in $CDCl_3$ at 300 MHz, chemical shifts in parts per million and coupling constants (J) in hertz. [b] *cis*-**20** was synthesized from dihydrodiol **16**. [c] Proton buried in aromatic region (7.6–7.7).

K-Region Derivatives. BgCh has a single K region at the 9,10-positions, and C_9 forms part of a bay region. As this is a region of the hydrocarbon of metabolic interest, the K-region *trans*-9,10-dihydrodiol was synthesized, resolved, and assigned absolute configuration. As reported by Clar,[24] the hydrocarbon can be oxidized to its 9,10-quinone by $Na_2Cr_2O_7$ in HOAc. Borohydride reduction[16,18a] provided a single dihydrodiol (±**22**) with $J_{9,10}$ = 2.9 Hz indicative of diaxial hydroxyl groups due to the proximate bay region.[17] Since the small value of $J_{9,10}$ is also consistent with a *cis*-dihydrodiol, assignment of trans stereochemistry resides primarily on the observation[25] that BgCh 9,10-oxide is enzymatically trans hydrated to the same compound by microsomal epoxide hydrolase.

Resolution of the racemic *trans*-9,10-dihydrodiol (±**22**) was achieved by HPLC as its diesters with ((−)-menthyloxy)acetic acid (α = 1.18). On the basis of physical correlations with other resolved and assigned K-region dihydrodiols,[18a] the less polar (early eluting from a silica column with ether in cyclohexane) diastereomer was expected to have 9*R*,10*R* absolute configuration. In all K-region cases examined thus far,[18a] the less polar *R*,*R* diastereomer has a larger negative $[\alpha]_D$ than the *S*,*S* diastereomer (−654° versus +508° here), shows a lower degree of magnetic nonequivalence between the diastereotopic $-OCH_2CO-$ hydrogens in the (menthyloxy)acetate groups than the *S*,*S* diastereomer ($\Delta\delta$ = 8–9 Hz versus 22–35 Hz here), and provides the negative dihydrodiol ($[\alpha]_D$ −795° here) when the hydroxyl groups prefer the diaxial conformation.

CD experiments were utilized to definitively establish assignment of absolute configuration to the *trans*-9,10-dihydrodiol. Recently Verdine and Nakanishi[26] have introduced the use of *p*-(dimethylamino)cinnamates in exciton chirality experiments since esters of this acid have an intense absorption band in the region of 361 nm. As the 9,10-dihydrodiol has essentially no absorption in this region (Figure 3, A), we reasoned that an exciton interaction between two such ester groups on the 9,10-dihydrodiol would provide evidence for its chirality. A solution of the (−)-9,10-dihydrodiol (1 mg, from less polar diastereomer), (*p*-(dimethylamino)cinnamoyl)imidazole (4 mg), and sodium hydride (0.2 mg) was stored in THF at 25 °C for 10 min. Workup and HPLC (Du Pont Zorbax

(23) Sayer, J. M.; Lehr, R. E.; Whalen, D. L.; Yagi, H.; Jerina, D. M. *Tetrahedron Lett.* **1982**, *23*, 4431–4434. Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969; pp 214–217 and 304–306.

(24) Clar, E. *Polycyclic Hydrocarbons*, Academic Press: New York, 1964; Vol. 1, pp 264–268.

(25) Grossman, S. J.; Jerina, D. M., in preparation.

(26) Verdine, G. L.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1093–1095.

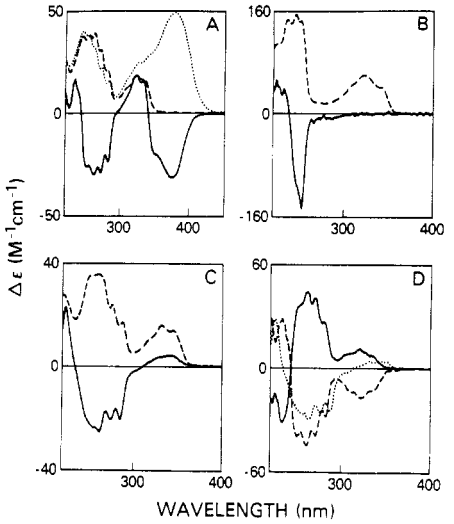
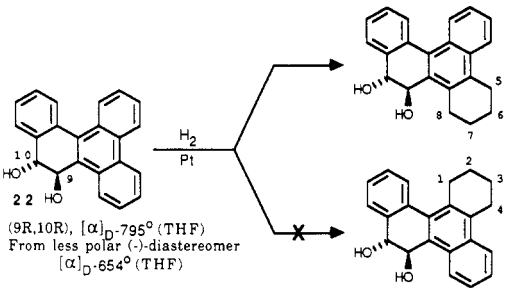


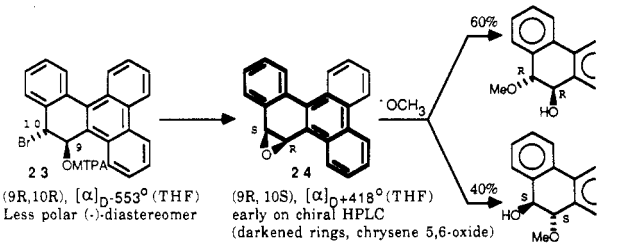
Figure 3. (A) Circular dichroism spectrum (solid line) of the bis(*p*-(dimethylamino)cinnamate) of the (−)-(9*R*,10*R*)-dihydrodiol compared with its UV spectrum (dotted line) and that of the free dihydrodiol (dashed line). All spectra were in acetonitrile. Concentration of the CD sample was based on an ϵ_{262nm} of 36 600 for the free dihydrodiol in tetrahydrofuran. (B) Circular dichroism (solid line) and UV spectra (dashed line) in tetrahydrofuran of the 5,6,7,8,9,10-hexahydrodiol obtained on reduction of the (−)-(9*R*,10*R*)-dihydrodiol. Concentration of the CD sample (λ_{max} 322 nm) was estimated from the value ϵ_{316nm} = 13 000 for the diacetate of the *trans*-5,6-dihydrodiol from benzo[*c*]-phenanthrene.[27] (C) Circular dichroism (solid) and UV (dashed) spectra of BgCh 9,10-oxide in acetonitrile. The CD spectrum of the (−)-9*S*,10*R* enantiomer from the late-eluting bromo MTPA is shown. Values of $\Delta\epsilon$ are based on an ϵ_{262nm} of 36 500 in THF for the dihydrodiol. The (−)-9,10-oxide has $\Delta\epsilon_{263nm}$ = −25.0 M^{-1} cm^{-1}. Acetonitrile was used for the CD spectrum because of poor stability of the 9,10-oxide in THF. (D) Circular dichroism spectra (THF) of the minor, late-eluting 9-*O*-methyl ether adduct obtained from the (+)-9,10-oxide (solid), the (−)-bis-MOA diester of the (−)-(9*R*,10*R*)-dihydrodiol (dashed), and the (−)-(9*R*,10*R*)-dihydrodiol (dotted).

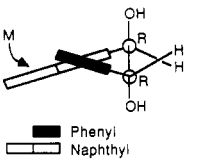
Reliance ODS, 4.6 × 100 mm, 2 mL/min with 90% CH_3CN in water, t_R 3.5 min) provided the desired diester (H_9 δ 6.95 and H_{10} δ 6.22 with $J_{9,10}$ = 2.7 Hz in THF-d_8; MS (CI, NH_3), M + 1 659), which has an intense absorbance band at 370 nm in THF (Figure 3, A). Although the CD spectrum of this diester (Figure 3, A) showed an intense negative band at $\Delta\epsilon_{375nm}$ = −31.8 M^{-1} cm^{-1}, consistent with *R,R* absolute configuration, the curve passed through 0 at 341 nm rather than the desired null point of 361 nm and was not symmetric with the positive band at 324 nm ($\Delta\epsilon_{324nm}$ = 18.9 M^{-1} cm^{-1}). Interaction between the dihydrodiol chromophore and one or both of the *p*-(dimethylamino)-cinnamates, at least in part due to the diaxial nature of these substituents, rendered the assignment of 9*R*,10*R* absolute configuration tentative. As an alternative approach, the (−)-9,10-dihydrodiol was reduced with hydrogen in the presence of platinum with the expectation that either the 1,2,3,4-benzo ring or the 5,6,7,8-benzo ring would be saturated (Scheme VIII). Both NMR and UV evidence (see Experimental Section) indicated that the 5,6,7,8-benzo ring had been saturated to produce an alkyl substituted analogue of the resolved and assigned BcPh *trans*-5,6-dihydrodiol.[18a] The CD spectrum (Figure 3, B) of the reduced 9,10-dihydrodiol (diaxial hydroxyl groups) is essentially identical (negative CD band corresponding to left-handed helicity) with that of the diaxial di-MTPA ester of the (5*R*,6*R*)-dihydrodiol of BcPh,[27] thus establishing that the (−)-9,10-dihydrodiol has 9*R*,10*R* absolute configuration.

Scheme VIII



Scheme IX





Agarwal et al.[28] have described the synthesis of BgCh 9,10-oxide via the halohydrin route[29] in which the parent hydrocarbon is converted to a *trans*-bromohydrin acetate (NBA in HOAc) and cyclized with base. This route was found amenable to the synthesis of optically active BgCh 9,10-oxide. Free bromohydrin was obtained by reduction of the acetate with DIBAL-H, and diastereomers were produced by reaction with the acid chloride of (−)-MOA and (−)-MTPA. Although conditions for separation of the MOA diastereomers were not found, the MTPA diastereomers were readly separated by HPLC (α = 1.23). Direct treatment of each diastereomer with dry sodium methoxide in THF provided the desired optically active 9,10-oxides.

The less polar (early eluting) bromo MTPA (−)-diastereomer (**23**, Scheme IX) was tentatively assumed to have *R,R* absolute configuration on the basis of an NMR correlation with related compounds[18a,30] since the hydrogen on the bromine-bearing carbon (H_{10} δ 5.50) appears at higher field relative to the (+) diastereomer (H_{10} δ 5.68). Thus, the (+)-9,10-oxide **24** (CD spectrum of the (−) enantiomer, Figure 3, C) would have 9*R*,10*S* absolute configuration (Scheme IX). The only other resolved and assigned K-region arene oxide which forms part of a bay region is the 5,6-oxide of chrysene.[30] In both cases, the enantiomer that has an *R*-benzylic oxirane carbon in the bay region (5*R* for chrysene and 9*R* for BgCh) has a positive $[\alpha]_D$ and a major, positive CD band below 300 nm. Notably, however, the (+)-(5*R*,6*S*)-oxide from chrysene is the late-eluting enantiomer on the chiral HPLC system described. As we had pointed out earlier, insufficient examples are available to allow prediction of absolute

(27) Sayer, J. M.; van Balderen, P. J.; Yeh, H. J. C.; Jerina, D. M. *J. Org. Chem.* **1986**, *51*, 452–456.

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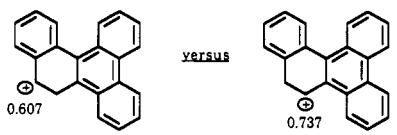
(29) van Bladeren, P. J.; Jerina, D. M. *Tetrahedron Lett.* **1983**, *24*, 4903–4906.

(30) Balani, S. K.; van Bladeren, P. J.; Cassidy, E. S.; Boyd, D. R.; Jerina, D. M. *J. Org. Chem.* **1987**, *52*, 137–144.

configuration based on elution order of enantiomers of arene oxides from these columns.[30]

More definitive evidence that the (+)-9,10-oxide has 9*R*,10*S* absolute configuration was obtained by nucleophilic addition of methoxide to form a pair of monomethyl ethers of the *trans*-9,10-dihydrodiol (Scheme IX). The adducts have practically mirror image CD spectra; 9-*O*-methyl $\Delta\epsilon_{262nm} = +44.4\ M^{-1}\ cm^{-1}$, 10-*O*-methyl $\Delta\epsilon_{262nm} = -52.5\ M^{-1}\ cm^{-1}$ (Figure 3, D). The CD spectrum of the 10-*O*-methyl ether is similar in shape and sign to that of the bis-MOA of the (−)-(9*R*,10*R*)-dihydrodiol (Figure 3, D), as is required for inversion of configuration at C_{10} of the (9*R*,10*S*)-oxide. The (−)-(9*R*,10*R*)-dihydrodiol has a similar but negative CD spectrum ($\Delta\epsilon_{264nm} = -29.9\ M^{-1}\ cm^{-1}$, Figure 3, D) in this region, as does the less polar (−)-bromo/MTPA precursor ($\theta_{276nm} = -4.1$ mdeg for a 1 OD solution at 252 nm in THF) of the (+)-9,10-oxide. These results require that the (+)-oxide has 9*R*,10*S* absolute configuration and firmly correlate the resolved dihydrodiol with the optically active oxide.

The observation that attack by methoxide occurs more readily at C_{10} (60%) compared to attack at C_9 (40%) is of interest in that Dewar PMO calculations of $\Delta E_{deloc}/\beta$[23] indicate that a carbocation at C_9 is more stable than one at C_{10}. The same situation pertains for chrysene 5,6-oxide



where attack by methoxide occurs more readily at C_6.[30] Although increased steric hindrance in the bay region may explain these unusual results (C_9 and C_5 in the BgCh and chrysene oxides, respectively), *tert*-butylthiolate in methanol preferentially attacks chrysene 5,6-oxide at the presumably more hindered 5-position (unpublished).

Studies are currently in progress to evaluate the mutagenicity and tumorigenicity of BgCh, its dihydrodiol, K-region oxide, and benzo-ring diol epoxides.[31]

Experimental Section

Melting points were obtained on a Kofler microscope melting point apparatus and are uncorrected. Mass spectra were obtained on a Hewlett-Packard 5985 quadrupole mass spectrometer at 12 or 70 eV, on a Kratos MS25RF mass spectrometer, or on a VG Model ZAB-E organic mass spectrometer. Exact mass spectra were obtained on a VG Model ZAB-E organic mass spectrometer using glycerol as a standard. ^1H NMR spectra (300 MHz) were obtained on a Varian XL-300 spectrometer using $Si(CH_3)_4$ or $CHCl_3$ as internal standard. Ultraviolet spectra were obtained by using a Perkin-Elmer Lambda 3 spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Rates of reaction were followed spectrophotometrically on a Cary 219 spectrophotometer and/or by HPLC on a Perkin-Elmer Series 4 liquid chromatograph. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tn. 3,4-Dihydrotriphenylen-1(2*H*)-one was prepared by Cambridge Chemical Company. THF was dried by refluxing and distilling from calcium hydride or sodium–benzophenone. Dry CCl_4 was prepared by distillation from calcium sulfate and storing over molecular sieves. Dry *p*-dioxane was prepared by filtration through alumina and distillation from calcium hydride. *p*-Dioxane used in kinetic experiments was distilled from sodium and stored frozen. Routine workup includes drying ($MgSO_4$), filtering, and removing solvents under reduced pressure. Amberlite (OH) ion-exchange resin was purchased from Aldrich Chemical Co. and washed thoroughly with dry THF before use. Purified *m*-CPBA was prepared by washing with a pH 7.5 buffer and drying from CH_2Cl_2. All other reagents and solvents were of reagent grade and were used without further purification.

12-(3-Carbomethoxy-2-propenyl)-12-hydroxy-9,10,11,12-tetrahydrotriphenylene (2). To a flame-dried 300-mL three-necked round-bottomed flask fitted with a condenser and two addition funnels were added 5.0 g (20.3 mmol) of 3,4-dihydrotriphenylen-1(2*H*)-one (1), 7.5 g (114.7 mmol) of zinc powder, dry THF (20 mL), and a few I_2 crystals. To one of the addition funnels was added 5.5 mL (42.1 mmol) of methyl 4-bromocrotonate in THF (40 mL) and to the other I_2 in THF. The bromocrotonate was added dropwise over 105 min at 45 °C, under N_2, with periodic addition of I_2. The reaction was quenched by addition of ice-cold 20% aqueous NH_4Cl (100 mL). Water was added and the aqueous solution extracted with PhH (3 × 100 mL) followed by routine workup. Normally this material was used without further purification. Pure material was isolated by chromatography on silica gel (eluting with 5% EtOAc in PhH) and was recrystallized from CH_2Cl_2–petroleum ether to give a white solid of mp 149–151 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.93–2.01 (m, H_{10}), 1.93–2.01 (m, $H_{11\alpha}$), 2.13–2.25 (m, $H_{11\beta}$), 2.86 (ddd, $H_{13\beta}$), 3.16–3.29 (m, H_9), 3.50 (ddd, $H_{13\alpha}$), 3.72 (s, H_{17}), 5.91 (d_{br}, H_{15}), 7.10 (m, H_{14}), 7.56–7.71 (m, $H_{2,3,6,7}$), 8.09 (dd, H_8, *J*'s = 7.5, 2.1), 8.64–8.78 (m, $H_{4,5}$), 9.02–9.09 (m, H_1); $J_{13\alpha,13\beta} = 14.9$, $J_{13\alpha,14} = 7.0$, $J_{13\alpha,15} = 1.5$, $J_{13\beta,14} = 8.2$, $J_{13\beta,15} = 1.3$, $J_{14,15} = 15.6$ Hz; mass spectrum (12 eV), *m*/*z* (relative intensity) 346 (M^+, 0.2), 328 (4.4), 247 (100), 229 (8.1), 218 (7.3), 191 (7.2).

12-(3-Carbomethoxy-2-propenylidene)-9,10,11,12-tetrahydrotriphenylene (3). A solution of crude 2, 650 mL of PhH, and ca. 2.0 g of *p*-TsOH was stirred overnight at room temperature under N_2. The solution was extracted with H_2O (3 × 500 mL), and routine workup gave an oily orange mixture of the diene products, which was used without further purification. Product purified by chromatography gave the following spectral data: ^1H NMR (major isomer) (300 MHz, $CDCl_3$) δ 2.11 (quintet, H_{10}, J_{app} = 6.5), 2.98 (t, H_{11}, J_{app} = 6.5), 3.20 (t, H_9, J_{app} = 6.5), 3.79 (s, H_{17}), 5.93 (d, H_{15}, $J_{15,14}$ = 15.1), 6.57 (d, H_{13}, $J_{13,14}$ = 11.7), 7.55–7.71 (m, $H_{2,3,6,7}$), 7.93 (dd, H_{14}), 8.10 (dd, H_8, *J*'s = 6.6, 2.7), 8.33 (d, H_1, *J* = 7.9); mass spectrum (12 eV), *m*/*z* (relative intensity) 328 (M^+, 100), 313 (6), 296 (10), 269 (19), 268 (14), 255 (20), 254 (9), 242 (17).

1-Triphenylenebutyric Acid (4). Crude 3 (8.56 g) was taken up in 10% KOH in ethylene glycol (175 mL) and degassed by several freeze–thaw cycles. The reaction flask was fitted with a reflux condenser and the solution heated to 185–190 °C for 15–18 h under N_2, diluted with H_2O (250 mL), and extracted with PhH (350 mL). The aqueous phase was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 200 mL). Routine workup produced 6.4 g of 4 (>90% pure) as a light yellow solid of mp 125–128 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (quintet, H_{14}, J_{app} = 7.8), 2.46 (t, H_{15}, J_{app} = 7.2), 3.40–3.47 (m, H_{13}), 7.50–7.70 (m, $H_{2,3,6,7,10,11}$); $H_{1,4,5,8,9}$, 8.43 (d, 1 H, *J* = 7.5) and 8.47–9.62 (m, 4 H); mass spectrum (12 eV), *m*/*z* (relative intensity) 314 (M^+, 100), 269 (4), 255 (13), 254 (12), 241 (24), 229 (24), 228 (91).

13,14-Dihydrobenzo[*g*]chrysen-11(12*H*)-one (5). A solution of 4 (5.81 g) in CH_3SO_3H (60 mL) was heated (55–60 °C) for 4 h with stirring under N_2. The mixture was cooled to room temperature, poured onto ice, diluted with H_2O, and extracted with CH_2Cl_2 (2 × 250 mL) which was back-extracted with H_2O (3 × 500 mL). Routine workup followed by flash chromatography on silica gel with CH_2Cl_2 produced 3.60 g (12.2 mmol, 60% overall yield from 1) of pure 5 as a solid of mp 54–56 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (quintet, H_{13}, J_{app} = 6.6), 2.81 (t, H_{12}, J_{app} = 6.6), 3.70 (t, H_{14}, J_{app} = 5.7), 7.50–7.72 (m, $H_{2,3,6,7}$), 8.35 (d, H_{10}, $J_{10,9}$ = 8.7); $H_{1,4,5,8,9}$, 8.43 (d, 1 H, *J* = 7.8) and 8.55–8.65 (m, 4 H); mass spectrum (70 eV), *m*/*z* (relative intensity) 296 (M^+, 100), 268 (8), 267 (11), 254 (20), 253 (20), 252 (19), 240 (75), 239 (94), 237 (23), 119 (46). Elemental anal. Calcd for $C_{22}H_{16}O$: C, 89.16; H, 5.44. Found: C, 88.95; H, 5.50.

11-Hydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (6). To a stirred, cooled (ice bath) solution of 9.1 g (30.8 mmol) of 5 in THF (150 mL) and MeOH (300 mL) was slowly added 5.84 g (154 mmol) of $NaBH_4$. The reaction mixture was allowed to warm to room temperature under N_2, and after 1 h, H_2O (400 mL) was added, followed by concentrated HCl. The aqueous mixture was extracted with CH_2Cl_2 (500 and 200 mL) which was back-

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extracted with H_2O (2 × 500 mL). Routine workup produced **6** as a very pure cream-colored solid (8.60 g, 28.8 mmol, 94%) of mp 172–174 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–1.90 (m, H_{13}), 1.98–2.10 (m, H_{12ax}), 2.20–2.32 (m, H_{12eq}), 3.34–3.45 (m, H_{14ax}), 3.66 (dt, H_{14eq}, J_{gem} = 15.5, J_{other} = 5.3), 5.06 (t_{br}, H_{11}, J_{app} = 5.5), 7.52–7.67 (m, $H_{2,3,6,7}$), 7.78 (d, H_{10}, $J_{10,9}$ = 8.4), 8.47–8.65 (m, $H_{1,4,5,8,9}$); mass spectrum (12 eV), *m/z* (relative intensity) 298 (M^+, 100), 280 (49), 270 (19), 255 (8).

13,14-Dihydrobenzo[*g*]chrysene (7). A solution of **6** (8.53 g, 28.6 mmol) and *p*-TsOH (2 g) in PhH (1 L) was stirred at room temperature under N_2 for 12–18 h and then extracted with H_2O (3 × 600 mL). Routine workup followed by flash chromatography on silica gel (loading with $CHCl_3$ and eluting with petroleum ether) gave 8.02 g (28.6 mmol, 100%) of pure **7** as a white solid of mp 137–138 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 2.20–2.29 (m, H_{13}), 3.55 (t, H_{14}, J_{app} = 7.9), 6.19 (dt, H_{12}, $J_{12,11}$ = 9.4, $J_{12,13}$ = 4.5), 6.72 (dt, H_{11}, $J_{11,12}$ = 9.4, $J_{11,13}$ = 1.6), 7.38 (d, H_{10}, $J_{10,9}$ = 8.3); $H_{1,4,5,8,9}$, 8.28 (dd, 1 H, *J*'s = 8.0, 1.1), 8.46 (d, 1 H, *J* = 8.4), and 8.51–8.64 (m, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 280 (M^+, 100), 279 (59), 278 (74), 277 (49), 276 (44), 265 (38), 252 (15), 138 (58).

Benzo[*g*]chrysene (8). To a solution of 150 mg (0.536 mmol) of **7** in dry PhH (20 mL) was added 146 mg (0.594 mmol) of *o*-chloranil. After 24 h at room temperature, the reaction was incomplete, so additional *o*-chloranil was added over a 48-h period (350 mg, 1.4 mmol). The reaction mixture was diluted with PhH (50 mL) and extracted with 5% NaOH (3 × 50 mL). Routine workup followed by flash chromatography on silica gel with petroleum ether gave pure **8** whose NMR spectrum was identical with that reported for BgCh:[12] ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.77 (m, $H_{2,3,6,7,12,13}$), 8.00–8.08 (m, $H_{10,11}$), 8.60–8.79 (m, $H_{4,5,8,9}$), 8.89–9.00 (m, $H_{1,14}$).

11,12-Epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (9). To a solution of *m*-CPBA (862 mg, 3.07 mmol) in CH_2Cl_2 (75 mL) was added 5% $NaHCO_3$ (175 mL). The two-phase mixture was stirred vigorously for at least 15 min, followed by addition of 1.0 g (3.57 mmol) in **7** in CH_2Cl_2 (25 mL), while vigorous sitrring was maintained under N_2. After 50 min, the aqueous phase was removed and the organic phase extracted with 5% $NaHCO_3$ (2 × 150 mL). Routine workup gave a cream-colored foam. ^1H NMR analysis showed a complete conversion of the alkene to the epoxide; however, approximately 7% of the product had been converted to the *m*-CPBA adduct **10**. This material was used without further purification. Trituration with CH_2Cl_2 and petroleum ether gave **9** as a light yellow to white solid (with a trace of **10**) of mp 68–72 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.45–1.57 (m, $H_{13\beta}$), 2.49–2.57 (m, $H_{13\alpha}$), 3.38–3.57 (m, H_{14}), 3.80–3.89 (m, H_{12}), 4.11 (d, H_{11}, $J_{11,12}$ = 4.4), 7.51–7.72 (m, $H_{2,3,6,7,10}$); $H_{1,4,5,8,9}$, 8.35 (d_{br}, 1 H, *J*'s = 8.0, small), 8.49 (d, 1 H, *J* = 8.5), and 8.51–8.67 (m, 3 H); mass spectrum (70 eV), *m/z* (relative intensity) 296 (M^+, 100), 268 (11), 267 (15), 254 (46), 253 (49), 252 (40), 239 (29).

***trans*-11,12-Dihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (11).** Crude **9** (ca. 1 g) was dissolved in THF (100 mL) to which H_2O (100 mL) was added, and the solution was made acidic (concentrated HCl). The mixture was stirred at room temperature for 3 h, diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (2 × 200 mL). The organic phase was extracted once each with 150 mL of H_2O, 5% $NaHCO_3$, and H_2O. Routine workup gave a white foam. ^1H NMR analysis showed that the reaction was clean and complete, but contained 20% of the *cis*-diol **12**. To remove **12**, the crude product was dissolved in 200 mL of acetone and excess anhydrous copper sulfate powder was added. The mixture was then heated at reflux for 4 h, cooled, filtered, and concentrated. ^1H NMR analysis showed no *cis*-diol present; however, the product 11,12,13,14-tetrahydrobenzo[*g*]chrysene 11,12-acetonide (**13**) was approximately 40% relative to the *trans*-diol **11**, indicating that some of **11** had also been converted to **13**. It was later found that with careful monitoring by TLC the reaction could be stopped as soon as all of the *cis*-diol had reacted, reducing the loss of **11**.

The mixture of *trans*-diol **11**, adduct **10** (from the epoxidation), and **13** was separated by flash chromatography on silica gel. Elution with 5% EtOAc in PhH first removed **13** (468 mg) and then **10** (163 mg). The *trans*-diol **11** (523 mg, 47%) was removed by elution with EtOAc. Higher yields of the *trans*-diol (75%) were obtained when the acetonide reaction was monitored. ^1H NMR of **13** (300 MHz, $CDCl_3$): δ 1.40–1.53 (m, H_{13ax}), 1.51, 1.59 (s, 2 × CH_3), 1.95–2.05 (m, H_{13eq}), 3.36–3.46 (m, H_{14ax}), 3.52–3.64 (m, H_{14eq}), 4.70–4.75 (m, H_{12}), 5.43 (d, H_{11}, $J_{11,12}$ = 7.4), 7.52–7.67 (m, $H_{2,3,6,7,10}$); $H_{1,4,5,8,9}$, 8.40 (dd, 1 H, *J*'s = 8.2, small), 8.52 (d, 1 H, *J* = 8.4), and 8.54–8.64 (m, 3 H). Trituration with CH_2Cl_2 and petroleum ether gave **11** as a white solid of mp 189–192 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–1.82 (m, H_{13ax}), 2.14–2.24 (m, H_{13eq}), 2.42 (s_{br}, OH_{11}), 2.34 (s_{br}, OH_{12}), 3.50 (dt, H_{14ax}, J_{gem} = 16.4, $J_{14ax,13}$ = 5.0), 3.67–3.80 (m, H_{14eq}), 4.01–4.17 (m, H_{12}), 4.82 (d_{br}, H_{11}, $J_{11,12}$ = 7.5), 7.53–7.69 (m, $H_{2,3,6,7}$), 7.86 (d, H_{10}, $J_{10,9}$ = 8.5); $H_{1,4,5,8,9}$, 8.45 (d, 1 H, *J* = 8.9) and 8.55–8.67 (m, 4 H); mass spectrum (12 eV), *m/z* (relative intensity) 314 (M^+, 100), 296 (64), 270 (60), 267 (30), 257 (33), 253 (22), 241 (64).

***trans*-11,12-Diacetoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (14).** To a solution of 510 mg (1.62 mmol) of **11** in dry pyridine (5 mL) was added Ac_2O (20 mL), and the mixture was stirred under N_2 for 12–18 h. The reaction mixture was poured into ice-cold saturated Na_2CO_3 (150 mL) with stirring and addition of ice. The aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL) followed by back extraction of the organic phase with 1 M HCl (200 mL) and 5% $NaHCO_3$ (100 mL). Routine workup gave a light yellow foam (650 mg, quantitative). Precipitation from and trituration with CH_2Cl_2 and petroleum ether produced **14** as a white solid of mp 64–66 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.78–1.91 (m, H_{13ax}), 2.10–2.20 (m, H_{13eq}), 2.14 (s, OCH_3), 2.19 (s, OCH_3), 3.51–3.72 (m, H_{14}), 5.33–5.40 (m, H_{12}), 6.34 (d, H_{11}, $J_{11,12}$ = 5.3), 7.51–7.70 (m, $H_{2,3,6,7,10}$); $H_{1,4,5,8,9}$, 8.44 (dd, 1 H, *J*'s = 8.5, small) and 8.51–8.67 (m, 4 H); mass spectrum (70 eV), *m/z* (relative intensity) 398 (M^+, 4), 338 (48), 296 (100), 278 (32), 265 (13), 267 (13), 252 (25), 241 (15), 240 (15), 239 (33).

***trans*-11,12-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (16) by the Bromination Method.** (Note: the most consistent results were obtained by using the method described later for the **16(R,R)** enantiomer.) All glassware for this procedure was rinsed with dilute NH_4OH, distilled H_2O, and acetone and dried before use. A mixture containing 100 mg (0.25 mmol) of **14**, 227 mg (1.27 mmol) of NBS, 300 mg of dry Na_2CO_3, and dry CCl_4 (60 mL) was heated in a 55–60 °C oil bath for 4 h, filtered cold, and extracted with H_2O (100 mL). Routine workup produced a crude residue, whose ^1H NMR showed it to be a mixture of products, which was used without further purification. ^1H NMR data (300 MHz): see Table I. Mass spectrum of the dibrominated compounds **14c** and **14d**: *m/z* (^{81}Br, M^{+4}): 510 (512, 514), 492 (494, 496), 450 (452, 454), 432 (434), 416 (418), 372 (374), 336, 294, 263.

The crude product was dissolved in THF (15 mL), and DBN (0.8 mL) was added. The mixture was stored in a freezer under N_2 for 2 days and then stirred at 1 °C for 2 h. The dark mixture of solvent and solid residue was diluted with EtOAc (50 mL) and extracted with 0.1 M HCl (2 × 50 mL), 5% $NaHCO_3$ (50 mL), and H_2O (50 mL). ^1H NMR analysis of the product from routine workup showed it to be a mixture of the dihydrodiol diacetate **15** and aromatized material. The crude product was suspended in anhydrous grade MeOH (60 mL) and cooled (ice bath), and dry NH_3 gas was bubbled through the solution for 20 min. The flask was then fitted with a balloon and warmed to room temperature. After 15–18 h, the MeOH and NH_3 were removed under reduced pressure and the residue was taken up in EtOAc and extracted with H_2O (2 × 75 mL). Routine workup followed by flash chromatography on silica gel, loading with THF and eluting first with 50:50 EtOAc–petroleum ether followed by pure EtOAc, gave 35 mg of **16** (0.111 mmol, 44% from **14**). Trituration with CH_2Cl_2 and petroleum ether gave a slightly yellow solid of mp 150–153 °C dec: ^1H NMR (300 MHz, C_6D_6) δ 1.58 (d, OH_{11}), 1.89 (d, OH_{12}), 4.38–4.46 (m, H_{12}), 4.59 (dd, H_{11}), 5.95 (dd, H_{13}), 6.89 (dd, H_{14}), 7.25–7.45 (m, $H_{2,3,6,7}$), 7.91 (d, H_{10}), 8.24–8.39 (m, $H_{1,4,5,8,9}$); $J_{9,10}$ = 8.2, $J_{11,12}$ = 11.6, $J_{11,OH}$ = 5.2, $J_{12,OH}$ = 4.5, $J_{12,13}$ ~ 2.0, $J_{12,14}$ = 2.4, $J_{13,14}$ = 10.0; mass spectrum (12 eV), *m/z* (relative intensity) 312 (M^+, 100), 295 (19), 294 (76), 281 (14), 267 (17), 266 (64), 265 (15); UV (THF, λ_{max}, ϵ_{max}) 311 (7800), 298 (12 480), 274 (56 650), 266 (59 470), 251 (43 830).

***cis*-11,12-Dihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (12).** Dry NH_3 gas was bubbled through a cooled (ice bath) suspension of 1.58 g of crude *cis*- and *trans*-((*m*-chlorobenzoyl)oxy)-12-hydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (**10**) in anhydrous MeOH (200 mL). After 20 min, the reaction flask was sealed with a balloon and warmed to room temperature.

The mixture was stirred for 12–15 h, and then the MeOH and NH_3 were removed under reduced pressure. The residue was taken up in EtOAc (200 mL) and extracted once each with 200 mL of H_2O, 5% NaOH, and H_2O. Routine workup followed by flash chromatography on silica gel (loading with THF and eluting with EtOAc) gave 372 mg of pure **12** and 357 mg of a 50:50 mixture of **11** and **12**. The recovery was 66% from the crude **10**. Trituration of **12** with CH_2Cl_2 and petroleum ether gave a cream-colored solid of mp 181–183 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 1.80–1.92 (m, H_{13ax}), 1.99–2.10 (m, H_{13eq}), 2.46 (s_{br}, $OH_{11,12}$), 3.40–3.53 (m, H_{14ax}), 3.70 (dt, H_{14eq}, J_{gem} = 16.3, J_{other} = 4.8), 4.25–4.35 (m, H_{12}), 4.97–5.01 (m, H_{11}, $J_{11,12}$ = 4.5), 7.52–7.71 (m, $H_{2,3,6,7}$), 7.79 (d, H_{10}, $J_{10,9}$ = 8.6); $H_{1,4,5,8,9}$, 8.50 (d, 1 H, J = 8.8) and 8.55–8.70 (m, 4 H); mass spectrum (70 eV), m/z (relative intensity) 314 (M^+, 55), 296 (100), 270 (38), 267 (29), 254 (38), 253 (59), 252 (53), 241 (70), 240 (49), 239 (81), 126 (35).

Benzo[*g*]chrysene-11,12-dione (17). A solution of 351 mg (1.12 mmol) of **12**, 3.1 g (13.7 mmol) of DDQ, and dry *p*-dioxane (60 mL) was refluxed for 42 h, cooled to room temperature, diluted with PhH (250 mL), and extracted with 5% NaOH (4 × 200 mL). Routine workup followed by trituration with petroleum ether gave 264 mg (0.86 mmol, 77%) of pure **17** as a red solid of mp 179–182 °C subl: ^1H NMR (300 MHz, $CDCl_3$) δ 6.52 (d, H_{13}, $J_{13,14}$ = 10.6), 7.60–7.80 (m, $H_{2,3,6,7}$), 8.29 (d, H_{14}), 8.34 (d, H_{10}, $J_{10,9}$ = 8.4); $H_{1,4,5,8,9}$, 8.07 (d_{br}, 1 H, J's = 8.2, small) and 8.53–8.66 (m, 4 H); mass spectrum (70 eV), m/z (relative intensity) 308 (M^+, 3), 281 (22), 280 (100), 252 (39), 251 (20), 250 (47), 125 (42). Note: similar results were obtained with a mixture of **11** and **12**.

11,12-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (16) by the Quinone Method. To a stirred suspension of 260 mg (0.84 mmol) of **17** in absolute ethanol (60 mL) was added 559 mg (14.9 mmol) of $NaBH_4$ in portions. The mixture was stirred for 90 h while open to the air and then diluted with Et_2O (100 mL), poured onto ice, and extracted with H_2O (3 × 100 mL). The aqueous phases were combined and extracted with Et_2O (150 mL). Routine workup followed by flash chromatography on silica gel (loading with THF and eluting with EtOAc) gave 187 mg (0.60 mmol, 71%) of pure **16**. Oxidation to the quinone during chromatography lowered the overall yield of **16**. Trituration with CH_2Cl_2 and petroleum ether gave a slightly yellow solid of mp 150–153 °C dec: ^1H NMR, mass, and UV spectra as reported above. Elemental anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.31; H, 5.52.

Synthesis and HPLC Separation of the Diastereomeric *trans*-11,12-Bis(((−)-menthyloxy)acetoxy)-11,12,13,14-tetrahydrobenzo[*g*]chrysenes (18). A solution of 2.60 g (8.28 mmol) of **11** and dry pyridine (80 mL) was stirred at 0–2 °C for 1 h, and then 10 g (43.0 mmol) of ((−)-menthyloxy)acetyl chloride was added dropwise over 10–15 min. The mixture was stirred under N_2 for 22 h and then poured into cold (ice bath) 0.1 M HCl (400 mL), and EtOAc (300 mL) was added. The aqueous phase was then separated and the organic phase extracted with 0.1 M HCl (2 × 300 mL) and 5% $NaHCO_3$ (2 × 300 mL). Routine workup followed by flash chromatography on silica gel twice, each time eluting first with PhH and then 5% EtOAc in PhH, produced 6.21 g of slightly impure bis ester as a foam: mass spectrum (DCI, NH_3), m/z (relative intensity) 724 ($M + NH_4^+$, 4), 493 (61), 296 (29), 281 (52), 280 (35), 232 (100).

The diastereomeric menthyloxy esters were separated by preparative HPLC on a Du Pont Zorbax SIL column (2.12 × 25.0 cm), by loading with CH_2Cl_2 and eluting with 4.5% Et_2O in hexane (27.7 mL/min, α = 1.36). The less polar bis ester **18(R,R)** (2.37 g, 81% from **11**) was from the (+)-(*R,R*)-tetrahydrodiol: $[\alpha]^{18}_D$ −131° (*c* 0.495, THF); NMR spectrum (C_6D_6) two singlets at δ 4.12 and 4.23 (2 H each, $COCH_2O$). The more polar bis ester **18(S,S)** (2.49 g, 85% from **11**) was from the (−)-(*S,S*)-tetrahydrodiol: $[\alpha]^{18}_D$ −13° (*c* 0.547, THF); NMR spectrum (C_6D_6) two AB quartets with doublets centered at δ 4.04 and 4.29 (2 H, J = 16.3 Hz, $COCH_2O$) and at δ 4.17 and 4.22 (2 H, J = 8.35 Hz, $COCH_2O$). The bis esters were both foams that gave mass spectra similar to the racemic material (DCI, NH_3): m/z 724 ($M + NH_4^+$). Each of the diastereomers was shown to be >99% diastereomerically pure by analytical HPLC.

***trans*-(11*R*,12*R*)-Dihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (11(R,R)).** A suspension of **18(R,R)** (2.33 g, 3.30 mmol) in anhydrous MeOH (170 mL) was cooled (ice bath), and dry NH_3 gas was bubbled through it for 1 h. The flask was then sealed with a balloon, warmed to room temperature, and stirred for 25 h. The MeOH and NH_3 were then removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (150 mL) and extracted with H_2O (2 × 150 mL). Routine workup followed by column chromatography on silica gel (loading and eluting with EtOAc) gave 909 mg (2.89 mmol, 88%) of pure **11(R,R)**. Trituration with CH_2Cl_2 and petroleum ether produced a white solid of mp 174–176 °C: NMR and mass spectra as for racemic **11**; optical rotation $[\alpha]^{18}_D$ +16° (*c* 0.484, THF); circular dichroism spectrum gave $\Delta\epsilon_{263nm}$ = −4.5 in CH_3CN.

***trans*-(11*S*,12*S*)-Dihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (11(S,S)).** In the manner described for **11(R,R)**, 2.44 g (3.46 mmol) of **18(S,S)** was stirred with MeOH (170 mL) saturated with NH_3 to produce 919 mg (2.93 mmol, 83.7%) of **11(S,S)**. Trituration with CH_2Cl_2 and petroleum ether produced a white solid of mp 172–174 °C: NMR and mass spectra as for racemic **11**; optical rotation $[\alpha]^{18}_D$ −15° (*c* 0.517, THF).

***trans*-(11*R*,12*R*)-Diacetoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (14(R,R)).** In the manner described for racemic **14**, 884 mg (2.8 mmol) of **11(R,R)** was reacted with Ac_2O (40 mL) and dry pyridine (9 mL) to produce 1.099 g (2.76 mmol, 98%) of **14(R,R)** as a cream-colored foam. Precipitation from and trituration with CH_2Cl_2 and petroleum ether produced a white solid of mp 64–66 °C: NMR and mass spectra as for racemic **14**; optical rotation $[\alpha]^{18}_D$ −108° (*c* 0.491, THF).

***trans*-(11*S*,12*S*)-Diacetoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (14(S,S)).** In the manner described for **14(R,R)**, 903 mg (2.88 mmol) of **11(S,S)** was reacted with Ac_2O (42 mL) and pyridine (9.5 mL) to produce 991 mg (2.49 mmol, 86%) of **14(S,S)** as a cream-colored foam. Precipitation from and trituration with CH_2Cl_2 and petroleum ether produced a white solid of mp 63–65 °C: NMR and mass spectra as for racemic **14**; optical rotation $[\alpha]^{18}_D$ +108° (*c* 0.490, THF).

***trans*-(11*R*,12*R*)-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (16(R,R)).** N_2 was bubbled through a mixture of 204 mg (0.51 mmol) of **14(R,R)**, 457 mg (2.57 mmol) of NBS, 2.4 mg of AIBN, dry CCl_4 (45 mL), and 1.0 g of Na_2CO_3 for 15–20 min, and then a condenser was added and the mixture heated in a 60–65 °C oil bath for 7–8 h under N_2. The mixture was then cooled to room temperature and placed in an ice bath, and 2.4 mL (19.4 mmol) of DBN was added. The mixture was stirred at 0 °C for 4 h and then at room temperature for 12–15 h, producing a black solid residue. The reaction mixture was then diluted with EtOAc (150 mL) and extracted with saturated NaCl (2 × 150 mL), 0.1 M HCl (2 × 150 mL), and 5% $NaHCO_3$ (150 mL) followed by routine workup. At this point the crude *trans*-(11*R*,12*R*)-11,12-diacetoxy-11,12-dihydrobenzo[*g*]chrysene (**15(R,R)**) could be purified by chromatography on silica gel (eluting with 5% EtOAc in PhH). However, this compound is not very stable to these conditions and a significant loss of product is observed, so the best procedure was to use it without purification. Pure material was isolated as an oily foam: ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, OCH_3), 2.17 (s, OCH_3), 5.70–5.76 (m, H_{12}), 6.21 (dd, H_{13}), 7.41 (d, H_{14}), 6.34 (d, H_{11}), 7.53–7.71 (m, $H_{2,3,6,7,10}$); $H_{1,4,5,8,9}$, 8.29 (d, 1 H, J = 7.6) and 8.49–8.63 (m, 4 H), $J_{11,12}$ = 6.7, $J_{12,13}$ = 4.0, $J_{13,14}$ = 10.2; mass spectrum (70 eV), m/z (relative intensity) 396 (M^+, 5), 336 (15), 294 (100), 265 (17).

Crude **15(R,R)** was suspended in anhydrous MeOH (75 mL), and dry NH_3 gas was bubbled through the cooled (ice bath) mixture for 20 min. The flask was sealed with a balloon and the mixture stirred at room temperature for 12–15 h. The reaction mixture was concentrated and the residue dissolved in a mixture of THF and H_2O, diluted with EtOAc (125 mL), and extracted with H_2O (2 × 100 mL). Routine workup followed by flash chromatography on silica gel (loading with THF and eluting quickly with 75% EtOAc–25% petroleum ether (N_2 purged)) gave 75 mg (0.24 mmol, 47%) of pure **16(R,R)**. The product was isolated as an amber foam, which could be converted to a light yellow to white solid by trituration with a mixture of CH_2Cl_2 and petroleum ether (mp 164–167 °C dec): NMR and mass spectra as for racemic **16**; optical rotation $[\alpha]^{18}_D$ −58° (*c* 0.433, THF); circular dichroism spectrum gave $\Delta\epsilon_{320nm}$ = −11 in THF.

***trans*-(11*S*,12*S*)-11,12-Dihydroxy-11,12-dihydrobenzo[*g*]chrysene (16(S,S)).** In the manner described for **16(R,R)**, 203 mg (0.51 mmol) of **14(S,S)** produced 79 mg (0.25 mmol, 49%)

of **16(S,S)** as a light yellow to white solid of mp 161–164 °C dec: NMR and mass spectra as for racemic **16**; optical rotation $[\alpha]^{18}_D$ +59° (*c* 0.458, THF).

11α,12β-Dihydroxy-13α,14β-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (19). A solution of 47 mg (0.152 mmol) of **16**, THF (8 mL), distilled H_2O (8 mL), and 1 drop of concentrated HCl was stirred in a cold bath at 0–2 °C under N_2, and 33 mg (0.24 mmol) of *N*-bromoacetamide (NBA) was added in three portions over a 15-min period. The mixture was stirred for 2 h, diluted with EtOAc (40 mL), and extracted with H_2O (3 × 30 mL). After routine workup, the crude product was taken up in CH_2Cl_2, precipitated by addition of petroleum ether, decanted, and then washed with petroleum ether. Removal of trace solvents under high vacuum produced 49 mg (0.121 mmol, 80%) of pure 13β-bromo-11α,12β,14α-trihydroxy-11,12,13,14-tetrahydrobenzo[*g*]-chrysene (bromotriol) as a faint red solid of mp 90–93 °C. Note: significant amounts of 13,14-dibrominated material is formed if less than 50% H_2O is used in the reaction. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.55 (s_{br}, H_{11}, H_{12}), 4.68 (d_{br}, H_{13}, $J_{13,14}$ = 3.9, $J_{13,12}$ = small), 5.40 (t_{br}, H_{14}, $J_{13,14}$ = 3.9, $J_{14,OH}$ = 4.7), 5.67 (d_{br}, OH), 5.94 (d_{br}, OH), 6.81 (d, OH_{14}, J = 4.7), 7.60–7.79 (m, $H_{2,3,6,7}$), 7.92 (d, H_{10}, $J_{10,9}$ = 8.7), 8.71–8.88 (m, $H_{4,5,8,9}$), 9.38 (d, H_1, J = 8.1). Mass spectrum (DCI): *m/z* (relative intensity) 390 ($M^+ - H_2O$, 5), 375 (20), 375 (91), 374 (100), 373 (90), 372 (85), 311 (11), 296 (26), 294 (61), 293 (25), 292 (25), 281 (38), 263 (30), 232 (45).

A mixture of 13 g of Amberlite IRA-400 ($^-$OH) ion-exchange resin, 42 mg (0.103 mmol) of bromotriol, and enough dry THF to cover the Amberlite was stirred under N_2 for 24 h. The solvent was decanted and the resin washed with excess THF. Evaporation of the solvents gave a quantitative yield of **19** (34 mg) as a solid of mp 153–156 °C dec: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (dd, H_{13}), 3.74–3.89 (m, H_{12}), 4.20 (d, H_{14}), 4.63 (dd, H_{11}), 5.75 (d, OH_{11}), 5.84 (d, OH_{12}), 7.65–7.80 (m, $H_{2,3,6,7}$), 7.94 (d, H_{10}), 8.74–8.99 (m, $H_{1,4,5,8,9}$); $J_{9,10}$ = 8.6, $J_{11,12}$ = 8.7, $J_{11,OH}$ = 6.2, $J_{12,13}$ = 2.0, $J_{12,OH}$ = 4.8, $J_{13,14}$ = 4.1; mass spectrum (DCI, NH_3), *m/z* (relative intensity) 328 (M^+, 11), 311 (100), 293 (26), 263 (10), 220 (5), 205 (9), 90 (6), 71 (55), 58 (15); exact mass calcd for $C_{22}H_{16}O_3$ + 1 329.1178, found 329.1137 (–12.0 ppm).

(11*R*,12*S*,13*R*,14*S*)-11,12-Dihydroxy-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (19(R,S,R,S)). In the manner described for racemic **19**, 133 mg (0.426 mmol) of **16(R,R)** was reacted with NBA (65 mg, 0.473 mmol) in THF (24 mL) and H_2O (24 mL) containing 2 drops of concentrated HCl. This produced 165 mg (0.404 mmol, 95%) of (11*R*,12*S*,13*R*,14*S*)-13-bromo-11,12,14-trihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene as a faint red solid of mp 95–97 °C: NMR and mass spectra as for racemic bromotriol; optical rotation $[\alpha]^{18}_D$ –16° (*c* 0.437, THF).

From reaction of 157 mg (0.385 mmol) of (11*R*,12*S*,13*R*,14*S*)-bromotriol and 22 g of Amberlite ($^-$OH) ion-exchange resin in THF was obtained 123 mg (0.375 mmol, 97%) of **19(R,S,R,S)** as a solid. Precipitation from a mixture of THF, CH_2Cl_2, and petroleum ether gave a white solid of mp 138–140 °C dec: NMR and mass spectra as for racemic **19**; optical rotation $[\alpha]^{18}_D$ –92° (*c* 0.586, THF).

(11*S*,12*R*,13*S*,14*R*)-11,12-Dihydroxy-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (19(S,R,S,R)). In the manner described for **19(R,S,R,S)**, 132 mg (0.423 mmol) of **16(S,S)** produced 166 mg (0.407 mmol, 96%) of (11*S*,12*R*,13*S*,14*R*)-13-bromo-11,12,14-trihydroxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene as a faint red solid of mp 94–97 °C; NMR and mass spectra as for racemic bromotril; optical rotation $[\alpha]^{18}_D$ +16° (*c* 0.433, THF).

To 161 mg (0.395 mmol) of (11*S*,12*R*,13*S*,14*R*)-bromotriol was added 20 g of Amberlite ($^-$OH) ion-exchange resin in THF, producing 126 mg (0.384 mmol, 97%) of **19(S,R,S,R)** as a white solid of mp 139–141 °C dec: NMR and mass spectra as for racemic **19**; optical rotation $[\alpha]^{18}_D$ +90° (*c* 0.424, THF).

11α,12β-Dihydroxy-13β,14β-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (20). For this reaction all glassware was washed with dilute NH_4OH, distilled H_2O, and acetone and then dried prior to use. To a cooled (10 °C) solution of 47 mg (0.149 mmol) of **16** in dry THF (12 mL), under N_2, was added 39 mg (3.09 mmol) of purified *m*-CPBA. The mixture was stirred for 2.5 h, diluted with Et_2O (25 mL), and extracted with ice-cold 5% NaOH (3 × 30 mL). The organic layer was extracted once with ice-cold 5% $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The resulting solid was triturated with petroleum ether to give **20** as a light yellow solid (44 mg, 0.133 mmol, 89%) of mp 151–153 °C dec: ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.71 (d_{br}, H_{13}), 3.74–3.92 (m, H_{12}), 4.57 (d, H_{14}), 4.60–4.69 (m, H_{11}), 5.67 (d, OH_{12}), 5.83 (d, OH_{11}), 7.64–7.79 (m, $H_{2,3,6,7}$), 7.94 (d, H_{10}); $H_{1,4,5,8,9}$, 8.46 (d, 1 H, J = 7.8) and 8.67–8.82 (m, 4 H); $J_{9,10}$ = 8.6, $J_{11,12}$ = 8.8, $J_{11,OH}$ = 6.2, $J_{12,13}$ = 1.8, $J_{12,OH}$ = 4.9, $J_{13,14}$ = 4.4; mass spectrum (DCI, NH_3), *m/z* (relative intensity) 346 ($M + NH_4^+$, 21), 328 (M^+, 38), 313 (36), 312 (95), 310 (100), 295 (46), 283 (31), 282 (51), 281 (60), 265 (38), 253 (46), 252 (33), 220 (44), 205 (92), 199 (36), 156 (69), 139 (74), 71 (36); exact mass calcd for $C_{22}H_{16}O_3$ + 1 329.1178, found 329.1158 (–6.0 ppm).

(11*R*,12*S*,13*S*,14*R*)-11,12-Dihydroxy-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (20(R,S,S,R)). In the manner described for racemic **20**, 64 mg (0.205 mmol) of **16(R,R)** in dry THF (16 mL) was reacted with 533 mg (3.09 mmol) of pure *m*-CPBA to yield **20(R,S,S,R)** as a slightly yellow solid (48 mg, 0.146 mmol, 71%). Precipitation from a mixture of THF, CH_2Cl_2, and petroleum ether gave a slightly yellow solid of mp 169–171 °C dec: NMR and mass spectra as for racemic **20**; optical rotation $[\alpha]^{18}_D$ –22° (*c* 0.538, THF).

(11*S*,12*R*,13*R*,14*S*)-11,12-Dihydroxy-13,14-epoxy-11,12,13,14-tetrahydrobenzo[*g*]chrysene (20(S,R,R,S)). In the manner described for **20(R,S,S,R)**, 36 mg (0.115 mmol) of **16(S,S)** produced 36 mg (0.109 mmol, 95%) of **20(S,R,R,S)** as a white solid of mp 172–174 °C dec: NMR and mass spectra as for racemic **20**; optical rotation $[\alpha]^{18}_D$ + 20° (*c* 0.457, THF).

***trans*-11,12-Bis((4-(dimethylamino)benzoyl)oxy)-11,12,13,14-tetrahydrobenzo[*g*]chrysene (21).** To a solution of ca. 0.6 mg of tetrahydrodiol (from the early-eluting bis(menthyloxy) ester **18**) in dry THF were added 10 mg of 4-(dimethylamino)benzoyl chloride and 5 mg of NaH. The mixture was stirred for 4 h and then worked up by standard methods. The crude ester was purified by HPLC on a Zorbax Reliance ODS column (4.6 × 100 mm) eluting with 90% CH_3CN in H_2O at 1.5 mL/min (t_R = 3.5 min), which produced a white solid: ^{1}H NMR (300 MHz, CD_3CN) δ 5.60 (m, H_{12}), 6.59 (d, H_{11}, $J_{11,12}$ = 6.2); mass spectrum (CI, NH_3), *m/z* 609 (M^+ + 1); UV (CH_3CN, λ_{max}, ϵ_{max}) 264 (90 100), 313 (58 600); CD spectrum (see Figure 1).

Kinetic Hydrolysis of Diol Epoxides 19 and 20. Rates of hydrolysis were determined at 25 °C in 1:9 dioxane–water (ionic strength 0.1 M ($NaClO_4$) containing 10^{-3} M buffers (formic acid, acetic acid, CHES (2-(cyclohexylamino)ethanesulfonic acid), and CAPS (3-(cyclohexylamino)-1-propanesulfonic acid)). Pseudo-first-order rate constants were determined spectrophotometrically at 263 nm (for reactions at pH 3.6–5.3 (k_H)) in solutions containing 8.4×10^{-6} M **19** or 3.2×10^{-6} M **20**. Spontaneous hydrolysis (k_0) was carried out at pH 9 and 10 at two concentrations (1.67 and 3.33×10^{-6} M **19**, 1.20 and 2.41×10^{-6} M **20**) and was monitored by HPLC at 265 nm. Rates were determined by following the time-dependent decrease in the ratio of internal standard (*p*-nitrobenzyl alcohol 0.9 and 1.8×10^{-5} M) to a thioether derived from remaining epoxide. The thioether was formed by reaction of 0.3 mL of kinetic solution with 0.1 mL of 1 M mercaptoethanol buffer (50% as its sodium salt) for 10 min followed by neutralization with 0.05 mL of 1 M perchloric acid. Chromatography of 0.1 mL of the more concentrated reaction mixtures and 0.2 mL of the less concentrated was performed on a 4.6 × 250 mm Du Pont Zorbax ODS column at 1.0 mL/min with CH_3CN–MeOH–H_2O (30:15:55) for 25 min for **19** and MeOH–H_2O (60:40) for 14 min followed by a linear gradient to 100% MeOH in 10 min for **20**. Retention times (min) for products were as follows. For **19**: *trans*-**19** (11.8), standard (15), *cis*-**19** (17.0), and thioether (21.5). For **20**: standard (10), *trans*-**20** (12), thioether (14), and *cis*-**20** (21). These same concentrations and chromatographic conditions were used to determine the amount of *trans*- to *cis*-tetrols produced at pH 3.0, which was also used to calibrate the total recovery of tetrols from the k_0 reactions.

Tetrol Characterization. The *trans*-**19** and *cis*-**19** tetrols were produced by hydrolysis of 1.2 mg of **19** (under the above kinetic conditions) at pH 4.0 for 30 min (total volume 19 mL). The pH was then adjusted to ~6.5 and the solvent concentrated to ~1.0 mL under reduced pressure. The aqueous solution was extracted with EtOAc (2 × 2 mL), washed with H_2O and saturated NaCl, and dried (Na_2SO_4) and the solvent removed under reduced

pressure. The crude tetrols were purified and separated by HPLC on a 4.6 × 250 mm Du Pont Zorbax ODS column with 70% MeOH–H_2O at 1.5 mL/min (early (*trans*-**19**), late (*cis*-**19**)). Tetrol *trans*-**20** was produced by hydrolysis of 3 mg of **20** under the kinetic conditions at pH 2.5 for 30 min (37 °C, total volume 27 mL). Workup as for **19** produced the crude tetrol, which was purified by HPLC on a 9.4 × 250 mm Du Pont Zorbax ODS column with 70% MeOH–H_2O at 4 mL/min, k' = 1.25: mass spectrum (DCI, NH_3), 364 for (M + NH_4^+, 70), 346 (M + NH_4^+ – H_2O, 83), and 215 (100). Tetrol *cis*-**20** was synthesized from the reaction of 5 mg of dihydrodiol **16** in 0.5 mL of pyridine with 0.1 mL of 1 M OsO_4 (in pyridine) for 4 h (room temperature, dark). The reaction mixture was then treated with $NaHSO_3$ in H_2O–MeOH for 2 h (room temperature, dark), extracted with EtOAc (2 × 25 mL), washed with H_2O and saturated NaCl, and dried (Na_2SO_4). Removal of the solvent produced an off-white solid (~70% yield), which was determined to be >98% *cis*-**20** after acetylation and chromatographic separation from the tetraacetate of *cis*-**19**. All of the tetrols were acetylated in excess pyridine and Ac_2O and worked up under standard conditions to produce the tetrol tetraacetates whose NMRs were used to confirm the assignments to cis and trans isomers. ^1H NMR (300 MHz, $CDCl_3$) for *trans*-**19**: δ 2.32, 2.23, 2.20, 2.15 (s, OAc CH_3's), 5.20 (dd, H_{12}), 5.41 ($t_{apparent}$, H_{13}), 6.69 (d, H_{11}), 6.78 (d, H_{14}); $H_{2,3,6,7}$, 7.53–7.71 (m, 4 H), 7.95 (d, H_{10}); $H_{1,4,5,8,9}$, 8.56–8.62 (m, 4 H), 8.69 (d, 1 H, J = 8.5); $J_{9,10}$ = 8.3, $J_{11,12}$ = 8.3, $J_{12,13}$ = 2.7, $J_{13,14}$ = 3.7. For *cis*-**19**: δ 2.22, 2.20, 2.13, 2.05 (s, OAc CH_3's), 5.06 (dd, H_{13}), 5.85 (dd, H_{12}), 6.38 (d, H_{11}), 7.19 (d, H_{14}); 7.54–7.70 (m, 4 H, $H_{2,3,6,7}$), 8.01 (d, H_{10}); 8.52–8.68 (m, 5 H, $H_{1,4,5,8,9}$); $J_{9,10}$ = 8.0, $J_{11,12}$ = 3.6, $J_{12,13}$ = 9.7, $J_{13,14}$ = 2.2. For *trans*-**20**: δ 2.24, 2.15, 1.94, 1.93 (s, OAc CH_3's), 5.71 (dd, H_{12}), 5.74 (dd, H_{13}), 6.45 (d, H_{11}), 6.91 (d, H_{14}); 7.50–7.69 (m, 4 H, $H_{2,3,6,7}$), 8.11 (d, H_{10}); 8.54–8.67 (m, 5 H, $H_{1,4,5,8,9}$); $J_{9,10}$ = 8.3, $J_{11,12}$ = 6.1, $J_{12,13}$ = 2.5, $J_{13,14}$ = 5.6. For *cis*-**20**: δ 2.23, 2.13, 1.89, 1.47 (s, OAc CH_3's), 5.71 (dd, H_{12}), 5.84 ($t_{apparent}$, H_{13}), 6.67 (d, H_{11}); 7.45–7.68 (m, 5 H, $H_{2,3,6,7,14}$), 8.00 (d, H_{10}); 8.52–8.64 (m, 5 H, $H_{1,4,5,8,9}$); $J_{9,10}$ = 7.8, $J_{11,12}$ = 8.4, $J_{12,13}$ = 2.3, $J_{13,14}$ = 3.5. The tetrol tetraacetates *trans*-**19**, *cis*-**19**, and *trans*-**20** all gave mass spectra (DCI-NH_3) with M + NH_4^+ at 532.

***trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*g*]chrysene (±22).** A solution of BgCh (113 mg, 0.4 mmol) in glacial HOAc (40 mL) was allowed to react with $Na_2Cr_2O_7$ (364 mg) at 90 °C for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extract was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a quantitative mass recovery with the product (benzo[*g*]-chrysene-9,10-dione) being approximately 70% pure as judged by NMR. A portion of the quinone was purified by HPLC on a Du Pont Zorbax SIL column (21 × 250 mm) eluted with 1% MeOH and 15% EtOAc in hexane (9.9 mL/min, t_R 20 min), mp 253–255 °C. Although Clar has reported mp 237–238 °C, no experimental details were given.[24] ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (apparent t, 1 H, J ~ 7.6), 7.57 (apparent t, 1 H, J ~ 8.3), 7.62–7.83 (m, 5 H), 8.04 (dd, 1 H, J = 7.6, 1.5), 8.41 (d, 1 H, J = 8.3), 8.56–8.61 (m, 1 H), 8.65 (d, 1 H, J = 8.3), 9.38–9.41 (m, 1 H). HRMS (EI): M^+ 308.0829 (calcd for $C_{22}H_{12}O_2$ 308.0837); λ_{max} (MeOH) 257 nm with shoulders at 289 and 300 nm.

Crude quinone (34 mg) was reduced with KBH_4 (45 mg) in 1:1 2-propanol–THF (45 mL) for 3 h at 50 °C. The reaction was quenched with dilute phosphoric acid, and the product was extracted (2 × 75 mL) into EtOAc. Routine workup provided a yellow oil, which was purified by HPLC on a Du Pont Zorbax SIL column (21 × 250 mm) eluted with 0.8% MeOH in CH_2Cl_2 (9.9 mL/min, t_R 20 min). Based on starting hydrocarbon, an overall yield of 28 mg (42%) of the desired **±22** was obtained. The 9,10-dihydrodiol had an NMR spectrum (300 MHz, acetone-d_6–methanol-d_4) that showed H_9 δ 5.44 and H_{10} δ 4.88 with $J_{9,10}$ = 2.9 Hz and aromatic hydrogens at δ 7.3–8.9. Mass spectrum (CI, NH_3): 330 for (M + NH_4^+, 70), 312 (M + NH_4^+ – H_2O, 70), and 295 (100). The small value of 2.9 Hz for $J_{9,10}$ indicates that the dihydrodiol has diaxial hydroxyl groups as expected since it forms part of a bay region.[17] The dihydrodiol has ϵ_{262nm} = 36 500 and ϵ_{321nm} = 15 000 in THF.

Resolution of *trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*g*]chrysene (±22). A solution of racemic dihydrodiol (27 mg) in dry pyridine (1 mL) was allowed to react with ((–)-menthyloxy)acetyl chloride (60 mg) for 16 h at 4 °C. Standard workup provided a viscous oil, from which the individual diastereomers were obtained by HPLC on a Du Pont Zorbax Golden SIL column (6.4 × 100 mm) eluted at 3 mL/min with 3% Et_2O in cyclohexane. The separated diesters (34 mg less polar, 20 mg more polar) were >98% diastereomerically pure and had the following rotations in THF (3 mg/mL): k_1' (less polar) = 8.73, $[\alpha]_D$ –654°; k_2' (more polar) = 10.27, $[\alpha]_D$ +508°. NMR spectra (300 MHz, C_6D_6) of the diastereomers were recorded. For the less polar diester, H_9 δ 7.38 and H_{10} δ 6.54 with $J_{9,10}$ = 2.9 Hz were observed. The –OCH_2CO– methylene protons of the (menthyloxy)acetyl groups were diastereotopic and appeared as two pairs of AB quartets with doublets centered at δ 3.41 and 3.50 for one pair and δ 3.62 and 3.70 for the other pair with J_{gem} ~ 16.5 Hz. For the more polar diester (H_9 δ 7.36 and H_{10} δ 6.55 with $J_{9,10}$ = 3.0 Hz), these same doublets were centered at δ 3.39 and 3.53 for one pair and δ 3.60 and 3.73 for the other pair with J_{gem} ~ 16.4 Hz. The free dihydrodiols were liberated by treatment of each bis(menthyloxy)acetate with NaOMe (25 mg) in 5 mL of 30% THF in MeOH (10 min at room temperature). Standard workup followed by purification of each enantiomer by HPLC as described for the racemic dihydrodiol provided the pure isomers (rotations at 1.5 mg/mL in THF): for the less polar (–)-diastereomer, $[\alpha]_D$ –795°; from the more polar (+)-diastereomer, $[\alpha]_D$ + 789°.

Reduction of (–)-9,10-Dihydroxy-9,10-dihydrobenzo[*g*]-chrysene (22(R,R)). A solution of the (–)-9,10-dihydrodiol (1.2 mg from less polar diastereomer) in EtOAc (1 mL) containing 4.5 mg of platinum oxide was agitated under 3 atm of hydrogen at 25 °C for 3 days. HPLC indicated the presence of starting material (6.2 min) and a single product (5.5 min) in roughly equal amounts based on absorbance at 245 nm (Du Point Golden Series 6.4 × 100 mm SIL column eluted at 3.0 mL/min with 1.5% MeOH and 15% EtOAc in hexane). The product showed three strong UV bands (THF) at 237, 246 (max), and 252 nm along with a weaker band at 322 nm (341 nm sh), very similar to that reported for the diaxial di-MTPA ester of benzo[*c*]phenanthrene *trans*-5,6-dihydrodiol (244 and 320 nm)[27] but quite different from that of the diaxial chrysene *trans*-5,6-dihydrodiol (257 and 266 nm).[32] The most informative feature of the NMR spectrum (300 MHz, $CDCl_3$) is the upfield shift of H_9 from δ 5.44 in the starting dihydrodiol to δ 5.10 in the product whereas H_{10} shifts very little from δ 4.88 to 4.83 in the product. Reduction of the 5,6,7,8-ring results in a loss of edge deshielding for H_9 in the starting material. The mass spectrum (CI, NH_3) of the reduction product showed a base peak at m/z 334 corresponding to (M + NH_4^+) for the expected hexahydrodiol.

Optically Active Benzo[*g*]chrysene 9,10-Oxide (24). *trans*-9-Acetoxy-10-bromo-9,10-dihydrobenzo[*g*]chrysene was prepared by reacting BgCh (112.8 mg, 0.4 mmol) with NBA (57.3 mg) in HOAc (35 mL) containing LiOAc·$2H_2O$ (203 mg) at room temperature under N_2. The reaction was monitored by HPLC and required an overnight reaction time to reach completion. Standard workup and HPLC (Du Pont Zorbax SIL column (21.2 × 250 mm) eluted at 25 mL/min with 15% EtOAc in hexane) produced 81.5 mg (48%) of the bromo acetate and 51.7 mg (50%) of 10-bromobenzo[*g*]chrysene. Agarwal[28] has reported an 84% yield of bromo acetate after a 30-min reaction time under nearly identical conditions. ^1H NMR (300 MHz, $CDCl_3$) for 10-bromobenzo[*g*]chrysene: δ 7.63–7.79 (m, 6 H, $H_{2,3,6,7,12,13}$), 8.44–8.48 (m, 1 H), 8.57–8.61 (m, 1 H), 8.70–8.79 (m, 2 H), 8.81 (d, 1 H, J = 7.8), 8.93 (s, H_9), 8.89–8.96 (m, 1 H). Mass spectrum for 10-bromobenzo[*g*]chrysene (EI): m/z (relative intensity) 358 (M^{+2}, 80), 368 (M^+, 80), 276 (100), 138 (70). ^1H NMR (300 MHz, $CDCl_3$) for the bromo acetate: δ 1.54 (s, CO_2CH_3), 5.48 (d, H_{10}, J = 2.5), 6.90 (d, H_9, J = 2.5), 7.39 (m, 1 H), 7.48–7.57 (m, 2 H), 7.6–7.8 (m, 4 H), 8.00 (d, 1 H, J = 7.8), 8.04 (d, 1 H, J = 7.8), 8.58 (d, 1 H, J = 8.2), 8.78 (apparent t, 2 H, J ~ 8.5).

Free bromohydrin (89% yield) was obtained by treatment of the ester (0.2 mmol) with an excess of DIBAL-H (0.8 mmol) in THF (15 mL) at 0 °C for 30 min; H_9/H_{10} at δ 5.62 and 5.72 with $J_{9,10}$ = 2.4 Hz (acetone-d_6). The racemic bromohydrin (54 mg in 2.0 mL of pyridine) was converted into a pair of diastereomeric bis esters with the acid chloride (50 mg) of (–)-MTPA (2 h, room temperature), which were separated by HPLC on a Du Pont

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Zorbax SIL column (21.2 × 250 mm) eluted at 9.9 mL/min with 25% Et_2O in hexane (rotations in THF): 43 mg, less polar diastereomer, $k' = 2.52$, $[\alpha]_D$ −553°; 41 mg, more polar diastereomer, $k' = 3.11$, $[\alpha]_D$ +581°. The NMR spectrum (300 MHz, $CDCl_3$) of the less polar (−) diastereomer had H_9 δ 7.11 and H_{10} δ 5.50 with $J_{9,10} = 2.8$ Hz, and the more polar (+) diastereomer had H_9 δ 7.02 and H_{10} δ 5.68 with the same coupling constant. Treatment of either bromo MTPA ester (33 mg) with dry NaOMe (75 mg) in stirred THF (4 mL) overnight at room temperature provided the 9,10-oxide in 80% yield. The less polar (−) diastereomer gave **24** with $[\alpha]_D$ +418° (2 mg/mL, THF) whereas the more polar (+) diastereomer gave **24** with $[\alpha]_D$ −430° (2 mg/mL, THF). When racemic oxide was chromatographed on a covalently bonded dinitrobenzoyl-(*R*)-phenylglycine column (0.41 × 25 cm, Regis Chemical Co.) eluted at 3.0 mL/min with 0.33% EtOH and 0.17% CH_3CN in hexane, the enantiomers emerged at 15.0 and 16.9 min. (+)-Oxide from the less polar (−) diastereomer corresponds to the earlier (15.0 min) of these peaks.

Reaction of Benzo[*g*]chrysene 9,10-Oxide with Methoxide. Benzo[*g*]chrysene 9,10-oxide is quantitatively converted to a pair of methanol adducts (with UV spectra identical with that of the 9,10-dihydrodiol) on storage in 1 M NaOMe at 40 °C for 5 h. After standard workup, the adducts were separated by HPLC on a Du Pont Zorbax SIL column (0.95 × 25 cm) eluted with 1% methanol and 10% EtOAc in hexane: $k' = 2.50$, 60%, and $k' = 3.59$, 40%. Both adducts gave mass spectra (CI, NH_3) with m/e 344 corresponding to ($M + NH_4^+$). NMR spectra (300 MHz, acetone-d_6) for each had $J_{9,10} \sim 2.3$ Hz consistent with axial, trans substituents. These adducts must be trans since in acidic methanol an additional pair of cis adducts are formed. The major, early-eluting adduct (CH_3O at δ 3.30) has H_{10} at δ 4.52 shifted 0.36 upfield relative to the 9,10-dihydrodiol due to the methyl group and H_9 δ 5.54 (OH coupled) shifted 0.09 downfield and thus corresponds to the product from methoxide attack at C_{10} on the oxide. The minor, late-eluting adduct (CH_3O at δ 3.48) has H_9 at δ 5.19 shifted 0.26 upfield due to the methyl group and H_{10} δ 5.14 (OH coupled) and thus corresponds to methoxide attack at C_9 on the oxide. Rotations of the methanol adducts were measured at 1.2 mg/mL in THF. From (+)-oxide: major (less polar), 10-*O*-methyl, $[\alpha]_D$ −912°; minor (more polar), 9-*O*-methyl, $[\alpha]_D$ +850°. From (−)-oxide: major (less polar), 10-*O*-methyl, $[\alpha]_D$ +975°; minor (more polar), 9-*O*-methyl, $[\alpha]_D$ −870°.

A Study of the Stereochemistry of the Electrocyclic Ring Closure of Substituted Bisallenes to Substituted 3,4-Bisalkylidenecyclobutenes

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Received January 27, 1989

The stereochemistry of the quantitative electrocyclic ring closure of the bisallenes **5**, **8**, **11**, and *erythro*- and *threo*-**14** to the substituted 3,4-bisalkylidenecyclobutenes in solution at 65 °C in the presence of cuprous chloride (believed to be a radical-anion, chain process) and in the gas phase at 300–350 °C has been determined. With **5**, **8**, and **11** there is only modest stereoselectivity favoring the least sterically strained product. With *erythro*- and *threo*-**14** the electrocyclic ring closure occurs in a strictly conrotatory manner under both sets of conditions, again showing only modest selectivity for formation of the least sterically strained product. In view of the fact that neither the conrotatory nor the disrotatory motions between the ground states in the radical-anion process are allowed by orbital symmetry, the observed conrotatory motion is attributed to less of a steric interaction in the conrotatory process than in the disrotatory process. With **8**, **11**, and **14** the electrocyclic ring closure reactions are considerably less stereoselective in the solution-phase reactions in the presence of cuprous chloride. The extensive formation of **10**, **12**, and **15** and **17** in the ring-closure reactions of **8**, **11**, and **14e** and **14t** suggest that the reactions occur via rather early transition states in which very little of the final steric strain energy has been developed. The results of theoretical and thermodynamic calculations indicate that the 3,4-bisalkylidenecyclobutenes are highly enthalpically favored; thus, their formation is expected to occur via rather early transition states in these electrocyclic ring-closure reactions, with the transition states for the ring closure of the radical anions occurring earlier than those for the ring closure of the neutrals. A comparison is made with the butadiene–cyclobutene system in which butadiene is the enthalpically favored product. The electronic properties of the 3,4-bisalkylidenecyclobutenes are briefly discussed.

Introduction

The electrocyclic ring-opening reactions of substituted cyclobutenes to form substituted 1,3-butadienes have been extensively studied.[1] In general, the substituted 1,3-butadienes are highly thermodynamically favored except when the diene is highly strained,[2a,b] halogen substituted,[2c] or when the ring closure results in the formation of an aromatic system.[2d] These reactions occur in an exclusively conrotatory manner,[3] which is controlled by orbital symmetry.[4] Recent interest in the author's laboratories has

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